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AN ANALYSIS OF TWO HUNDRED AND TWENTY CASES OF ENDOCARDITIS

WITH SPECIAL REFERENCE TO THE SUBACUTE BACTERIAL TYPE *

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MINNEAPOLIS

The condition of the heart valves included in the term subacute bacterial endocarditis has within the last fifteen to twenty years created much interest. As early as 1885, Osler [1] described this condition in what he called malignant endocarditis. Horder [2] and Billings [3] described it, in 1909, under the heading of infective endocarditis. Endocarditis lenta was the term used by Schottmüller [4] in 1910, and in the same year the term subacute bacterial endocarditis was first used by Libman and Celler.[5] Munzer [6] and Ruggeri [7] used the term slow endocarditis. Various phases of the subject have been considered in France by Achard and Rouillard,[8] Debré,[9] and others; in Germany by Schottmüller,[4] Munzer,[6] Hassencamp [10] and Moravitz;[11] in England by Lewis,[12] Horder,[13] Poynton,[14] Boyd,[15] Cotton,[16] Combs,[17] Gibson,[18] Gow [19] and Starling;[20] in Canada by Murray and Lougheed;[21] and in the United States by Libman and Celler,[5] Baehr and Lande [22] and others.

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* From the Department of Pathology, University of Minnesota.

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An exact agreement among workers as to what is meant by subacute bacterial endocarditis has not been reached. Libman [23] has included such conditions as are frequently called chronic ulcerative endocarditis, chronic malignant endocarditis and endocarditis lenta. Valvular defects resulting from rheumatic and syphilitic infections and defects caused by congenital deformities and arteriosclerosis he would not consider as endocarditis. He would classify endocarditis as rheumatic, syphilitic and bacterial. The bacterial type he would divide into acute (lasting up to about six weeks) and subacute (lasting from four to eighteen months or more). Horder [24] would eliminate from the class subacute bacterial endocarditis such conditions as acute bacterial endocarditis, bacterial endocarditis associated with other diseases, acute or chronic and ulcerative endocarditis.

A general uniformity of opinion exists among writers on the subject of subacute bacterial endocarditis in regard to a group of clinical and pathologic findings. Clinically, the condition is characterized by an insidious onset, disability and loss of tone, sallow complexion, intermittent fever which is often not high and at times in the course of the disease may be absent for considerable periods, progressive anemia of the secondary type, joint pains and some articular swelling not so severe as in rheumatic fever, dyspnea, the presence of petechiae on the skin and conjunctivae, especially when they occur in recurrent crops, Osler's nodules, mild leukocytosis and the marked frequency of the finding of *Streptococcus viridans* in the blood. The disease seems to prevail among persons from 20 to 45 years of age and frequently in persons who have had a previous attack of rheumatism. This form is common among soldiers, as is pointed out by Becher [25] in Germany and Murray [21] in Canada. According to Hassencamp,[10] it is on the increase in Germany, especially among ex-soldiers. Lewis [12] thinks that it is much more common than has been generally believed and that it often escapes recognition. Moravitz [11] says that it is generally not diagnosed properly but is frequently called incipient tuberculosis, anemia, malaria, etc. In emphasizing the increased incidence since the war, Gow [19] shows that in an English hospital there were seventeen cases of subacute bacterial endocarditis in 460 necropsies during a period of seventeen months, while in the same length of time since the war there were thirty cases in 345 necropsies. Horder [24] found it occurring in England in the proportion of about 1 to 200 among patients admitted to the hospital in which he made his observations. This form of endocarditis seldom has

23. Libman, E.: Am. J. M. Sc. **144**:313, 1912.
24. Horder, T. J.: Brit. M. J. **2**:301, 1920.
25. Becher, E.: München. med. Wchnschr. **68**:267, 1921.

a duration of more than two to three years. It is generally fatal, although recoveries have been reported by Libman [26] and Murray.[27]

The characteristic pathologic findings at necropsy are: embolic processes (such as petechiae in the skin and conjunctivae, infarction of the spleen and kidneys, cerebral embolism and embolic glomerulonephritis), enlarged spleen, large and villous vegetations on leaflets otherwise normal or thickened from previous inflammation and involvement of the mural endocardium. Pericarditis and myocarditis are seldom found. Aschoff nodules in the myocardium are rare. *Streptococcus viridans* is commonly found in the heart blood and on the injured valves.

The purpose of this paper is to analyze 220 hearts which show the results of definite rheumatic or bacterial infections to determine whether a definite anatomic picture of subacute bacterial endocarditis exists and if so how it differs pathologically from other forms, such as primary and secondary acute bacterial and rheumatic endocarditis, and to study the origin and manner of development of old healed defective valves.

Two hundred and twenty hearts with infectious valvular injuries were found in a series of 3,890 necropsies performed at the University of Minnesota during the years 1912 to 1922. One hundred and thirty-six hearts had been preserved and were available for examination. The necropsy descriptions were used for the remaining eighty-four. From one to three slides of heart, kidneys and liver from each necropsy were examined. Only positive microscopic findings are conclusive, for it would be necessary to have sections from many different parts of organs in order to draw negative conclusions.

These 220 hearts were separated by necropsy findings into two main groups: hearts with active lesions and hearts with old healed defective valves. The cases with active lesions were further divided into: (1) bacterial endocarditis (those without an immediate association with rheumatism), and (2) rheumatic endocarditis (those immediately associated with acute rheumatic fever). The bacterial type was divided on the basis of the duration of the process into: (*a*) subacute bacterial endocarditis with a clinical course of more than six weeks (usually from four to eighteen months or more), and (*b*) acute bacterial endocarditis with a duration of not more than six weeks. The latter class was considered as primary acute bacterial endocarditis when no primary focus of infection existed and as secondary acute bacterial endocarditis when associated with another disease, acute or chronic.

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26. Libman, E.: Brit. M. J. **2**:304, 1920.
27. Murray, L. M.: Ann. Clin. Med. **1**:18, 1922.

The classification adopted as a working basis in analyzing these hearts was, therefore:

I. Hearts with active lesions.
   1. Bacterial endocarditis.
      (*a*) subacute.
      (*b*) acute (primary, secondary).
   2. Rheumatic endocarditis.

II. Hearts with old healed defective valves.

Fifteen cases of bacterial endocarditis were classified as doubtful because the duration of the disease was unknown. It is seen in Table 1 that, of the 220 hearts, the subacute bacterial group comprises seventy-two (33 per cent.), those with old healed valves sixty-four (29 per cent.), the secondary acute bacterial forty-three (20 per cent.), the primary acute bacterial seventeen (8 per cent.), and the acute rheumatic nine (4 per cent.).

TABLE 1.—*Relative Number of Each Kind of Valvular Disease Found in 220 Necropsies*

Kind	Number	Percentage
Subacute bacterial endocarditis	72	32.7
Healed thickened valves	64	29.0
Secondary acute bacterial endocarditis	43	19.5
Acute bacterial endocarditis, independent	17	7.7
Acute rheumatic endocarditis	9	4.0
Doubtful	15	6.8

Three thousand eight hundred and ninety necropsies were performed from 1912 to 1922. The total number of hearts with valvular disease was 220, or 5.6 per cent.

ILLUSTRATIVE CASES OF EACH GROUP

Subacute Bacterial Endocarditis.—A white boy, aged 18, admitted to the hospital on Aug. 5, 1920, complained of weakness and fever. At the age of 6 he had had rheumatic attacks with pain in the joints, and at 10 he had had measles and mumps. He had had frequent attacks of sore throat. In the winter of 1919-1920 he had had influenza and pneumonia. About March, 1920, he noticed pain in the region of the spleen followed by chills and fever coming on about 4 o'clock each afternon. Three weeks later he had attacks of precordial pain relieved by sitting up. Physical examination showed the heart to be enlarged and the spleen and liver palpable. The urine contained many leukocytes and red blood cells. The hemoglobin content was 31 per cent.; the erythrocytes numbered 2,660,000. A blood culture made before death yielded a pure growth of *Streptococcus viridans.* The temperature was septic in type, running up to from 102 to 103 F. each afternoon. During his stay in the hospital he developed at one time a left-sided hemiplegia. There was pain in the left arm and loss of radial pulse. He grew progressively worse until death on Oct. 4, 1920. When examined at necropsy no edema was present. There was no excess fluid in the peritoneal, pleural or pericardial cavities. The pericardium was adherent to the heart over the entire anterior surface, with fibrous adhesions. The heart weighed 540 gm. The mitral valve leaflets were almost entirely covered with numerous vegetations which extended up on the wall of the auricle. The spleen was enlarged, weighing 310 gm. and adherent to the

omentum. A number of hard white infarcts measuring up to 4 cm. in diameter were found. The liver was enlarged, weighing 2,200 gm., and on section passive congestion was evident. Over the surface of both kidneys puckered scars of healed infarcts were seen. On the right side of the brain, there was a depression which on section showed a softened area 1 cm. in diameter.

Healed Defective Valves.—A young white man, aged 27, admitted to the hospital on April 15, 1922, complained of hemoptysis, anasarca, precordial pains, dyspnea, weakness and palpitation. He had chorea at the age of 4, with recurrences until the age of 6, and measles without complications at the age of 9. His first attack of rheumatism occurred at the age of 19. It lasted a month and involved all the joints. They were red, swollen and painful. At the age of 22 he had had a second attack lasting three months. He had had frequent attacks of tonsillitis. Following his second attack of rheumatism in 1917 he had developed slight dyspnea and palpitation on exertion. This had cleared up in a short time. In August, 1921, while working, he had developed a troublesome cough and expectorated bright red blood. In January, 1922, he had had edema of the extremities for the first time. Because of extreme dyspnea and weakness he entered the hospital. He had to be propped up in bed to breathe. The skin was slightly icteric, and the mucous membranes were cyanotic. Death occurred on Oct. 1, 1922, from heart failure. At necropsy marked edema was present in the lower extremities, scrotum, penis, back, forearms and hands. The skin was yellow. The peritoneal cavity contained about 6 liters of straw colored fluid. The right pleural cavity contained 200 c.c. of yellowish fluid, and the left 500 c.c. About 900 c.c. of clear fluid were found in the pericardial cavity. The heart weighed 550 gm. The edges of the tricuspid valves were replaced by firm fibrous scar tissue. The orifice was greatly narrowed. The mitral orifice was also greatly narrowed and the leaflets fused, thickened and calcified. The aortic leaflets were distorted, but the orifice was not greatly narrowed. The lungs were edematous. The liver showed marked evidence of chronic passive congestion. The spleen and kidneys were free from infarcts.

Secondary Acute Bacterial Endocarditis.—A white woman, aged 36, was admitted to the hospital on May 25, 1921. On April 14, she had been delivered of a full term baby, but had not had an attending physician. The baby had died on April 24 from erysipelas and meningitis. On the twentieth day after delivery, the patient developed swelling in the legs and a temperature of 103 F. She died on May 31, 1921, from sepsis. At necropsy the left leg and thigh were found to be markedly edematous, and the foot and leg half way up to the knee were gangrenous. Some fibrinous adhesions were present in the pelvic cavity but no free pus. On the aortic cusps were numerous pink vegetations, some of which were large. The spleen was enlarged and contained two fresh infarcts. No infarcts were found in the kidneys. The uterus was soft and friable. A thin serous fluid was present on the uterine mucosa. The left common iliac vein was completely filled with a soft purulent thrombus. The uterine plexus showed thrombosis. Blood cultures made before death contained *Streptococcus hemolyticus.*

Primary Acute Bacterial Endocarditis.—A white woman, aged 34, who had always been well, was taken sick September 21, 1919, with a chilly sensation, nausea and pain in the back. She had no sore throat at the time. The temperature, which was 104 F., continued until death on Sept. 27, 1919. At necropsy no edema or jaundice was present. No lesions were noted in the pelvis or about the appendix. The heart weighed 370 gm. Several large vegetations were present on the mitral valve. The leaflets were thickened and the adjacent edges fused. On the leaflets of the aortic valve there were two or three rather large vegetations. The lungs showed a slight increase in amount of fluid. The spleen was large, weighing 520 gm. Several infarcts were found in the spleen and kidneys. From cultures of the heart blood and spleen *Streptococcus hemolyticus* was grown.

Acute Rheumatic Endocarditis.—A young white girl, aged 9, admitted to the hospital on Nov. 11, 1922, complained of dyspnea on exertion, nervousness and pain over the precordium. The present illness began in June, 1922, when she had an attack of acute rheumatism. There was multiple involvement. The joints were swollen, red and tender. The rheumatic attack lasted two weeks. The tonsils were enlarged and reddened. The temperature ranged from 99 to 101.5 F. The blood showed 70 per cent. of hemoglobin, 3,950,000 red blood cells and 13,000 white cells. On Dec. 2, 1922, she had a sudden collapse with marked dyspnea and cyanosis and died. At necropsy slight edema was noticed about the ankles and face. About 200 c.c. of clear fluid was present in the peritoneal cavity. The pleural cavities contained no excess fluid. The pericardial fluid was clear, but there were multiple fine nodules over the epicardial surface. Multiple small verrucose bodies with smooth surfaces were present on the under surface and on the edges of the mitral valves. Similar small globular structures were found on the under surface and on the edges of the cusps of the aortic valve and a few on the tricuspid. The lungs were grayish pink and feathery throughout. There was no evidence of infarcts in the spleen and kidneys. Blood cultures taken during life and at necropsy were negative.

TABLE 2.—*Age and Sex Incidence*

	Subacute Bacterial Endocarditis			Healed Thickened Valves			Secondary Acute Bacterial Endocarditis			Acute Bacterial Endocarditis, Independent			Acute Rheumatic Endocarditis		
Decade	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
1.....	0	1	1	1	0	1	1	0	1	0	0	0	0	2	2
2.....	5	5	10	1	0	1	2	0	2	1	2	3	0	3	3
3.....	13	4	17	7	4	11	1	8	9	2	1	3	2	1	3
4.....	12	5	17	11	3	14	4	7	11	1	1	2	0	0	0
5.....	14	1	15	13	3	16	5	2	7	1	2	3	1	0	1
6.....	7	2	9	11	2	13	4	3	7	3	0	3	0	0	0
7.....	2	0	2	4	1	5	4	1	5	2	1	3	0	0	0
8.....	1	0	1	1	0	1	0	0	0	0	0	0	0	0	0
9.....	..	..	..	2	0	2	1	0	1	0	0	0	0	0	0
Totals.	54	18	72	51	13	64	22	21	43	10	7	17	3	6	9

The ratio of males and females coming to necropsy is 2 : 1.

AGE INCIDENCE

In his cases, Horder [24] found subacute bacterial endocarditis occurring between the ages of 15 and 50. Half of them occurred between the ages of 20 and 40. In Debré's [9] analysis, 66 per cent. of the cases occurred in patients between the ages of 15 and 30. He also found a few cases in persons above 30 and a few in children. M'Cartney [28] reported a case in a child 3½ weeks old, and cited the case of an infant 6 months old. In our cases, it is seen in Table 2 that the peak of incidence of the subacute bacterial and the secondary acute bacterial groups is in the third and fourth decades, of the old healed valve group in the fourth and fifth decades and of the acute bacterial and acute rheumatic groups in the second and third decades. Comparing the age incidence in cases of old valvular defects with cases of hyper-

28. M'Cartney: J. Path. & Bacteriol. **25**:277, 1922.

tension hearts (with which they are apt to be confused clinically), it is found that the maximum age incidence in cases of hypertension hearts is in the sixth and seventh decades.[29]

SEX INCIDENCE

Males predominate in the subacute bacterial and old healed cases, while in the primary and secondary acute bacterial and acute rheumatic cases there is a prevalence of females. There is a high percentage of females in the secondary acute bacterial group, especially in the third and fourth decades. This is largely accounted for by the association of endocarditis with abortion and puerperal sepsis. This occurred nine times in the forty-three cases of secondary acute bacterial endocarditis. Rheumatic endocarditis is mainly a disease of youth but may occur later in life.

TABLE 3.—*Embolic Processes*

	Subacute Bacterial Endocarditis		Healed Thickened Valves		Secondary Acute Bacterial Endocarditis		Acute Bacterial Endocarditis, Independent		Acute Rheumatic Endocarditis	
	No.	%	No.	%	No.	%	No.	%	No.	%
Petechiae	21	29.0	3	4.7	2	4.6	3	18.0	1	11.0
Infarct, spleen	34	47.0	10	15.5	15	35.0	7	41.0	0	0.0
Infarct, kidney	30	42.0	7	11.0	10	23.0	7	41.0	0	0.0
Paralysis	12	17.0	1	1.5	1	2.3	2	11.8	0	0.0
Cases with embolic processes	48	67.0	14	22.0	16	37.0	10	59.0	1	11.0
Cases with all four forms	1	1.4	0	0.0	0	0.0	0	0.0	0	0.0
Cases with both spleen and kidney involvement	14	19.0	6	9.0	9	21.0	6	35.0	0	0.0
Cases of embolism on basis of spleen, kidney and brain	45	62.5	12	19.0	16	37.0	9	53.0	0	0.0
Total embolic processes	105	36.5	21	8.0	28	16.0	19	28.0	1	2.8
Embolic glomerulonephritis	35	55.0	2	4.0	1	2.5	2	12.0	0	0.0

EMBOLIC PROCESSES

The frequent occurrence of embolic processes in subacute bacterial endocarditis has been emphasized by practically all who have written on the subject. Starling [20] found them in 58 per cent. of his cases. Such processes are manifested before death as petechiae on the skin and conjunctivae, and by symptoms of cerebral embolism. At necropsy they are seen as infarcts of the spleen, kidneys and brain. The relative frequency of such processes is shown in Table 3. Petechiae were found by the clinician or pathologist in thirty-two (14.5 per cent.) of the 220 cases. Of these thirty-two cases exhibiting petechiae, twenty-one (29 per cent.) belonged to the subacute bacterial class, three (5 per cent.) to the class with healed defective valves, two (5 per cent.) to the secondary acute bacterial, three (18 per cent.) to the primary acute bacterial, and one (11 per cent.) to the acute rheumatic. This shows the percentage highest in the subacute and acute bacterial classes.

29. Bell, E. T.: Personal communication.

Petechiae occurred only once in the acute rheumatic group. As pointed out by Gibson,[18] too much diagnostic importance must not be placed on petechiae, even when they occur in recurrent crops, for they may appear in other pathologic conditions, such as septicemia.

The most frequent manifestation of arterial embolism found at necropsy is the presence of infarcts in the spleen. In Starling's [20] seventeen cases of subacute bacterial endocarditis coming to necropsy he found infarcts in the spleen in twelve. In the 220 spleens in our series, infarction was found in sixty-eight (31 per cent.). Its occurrence is more than twice as frequent as were the petechiae. As with the petechiae, the infarction of the spleen is more frequent in the subacute bacterial than in the other classes, but is relatively high in the acute forms. Infarcts were present in thirty-four (47 per cent.) of the subacute bacterial cases, in ten (15.5 per cent.) of the cases with old healed valves, in fifteen (35 per cent.) of the secondary acute bacterial, in seven (41 per cent.) of the primary acute bacterial, and in none of the acute rheumatic cases.

Infarction of the kidneys was common and of the embolic processes was next in frequency to infarction of the spleen. In many of the cases both kidneys showed infarcts, but in these statistics the presence of infarcts in either or both kidneys is reported as one. Infarction of the kidneys occurred fifty-seven times in the 220 cases, or in 26 per cent. of them, only a little less frequently than infarction of the spleen. It was present in thirty (42 per cent.) of the subacute bacterial cases, in seven (11 per cent.) of the cases of the old healed defective valves, in ten (23 per cent.) of the secondary acute bacterial, and in seven (41 per cent.) of the primary acute bacterial cases, but in none of the acute rheumatic cases was infarction of the kidneys noted. In discussing embolic processes in subacute bacterial endocarditis, Horder [13] states that the infarcts in subacute bacterial endocarditis are nonsuppurative, a characteristic which distinguishes them from the infarcts in the acute bacterial forms. The kidneys in forty-five subacute bacterial cases were examined for abscesses. In none of these was there any indication of abscesses. In ten of the kidneys of the thirty-two acute bacterial forms, abscesses were present. Abscesses were not found in the kidneys in any of the cases of acute rheumatic hearts. The findings show the more frequent occurrence of suppuration associated with the acute bacterial forms. The greater virulence of the organisms producing the acute bacterial forms as a rule will account for this.

Paralysis resulting from brain emboli was a frequent finding, occurring eighteen times (20 per cent.) in the hearts examined. It was found in the different classes as follows: in the subacute bacterial twelve (17 per cent.), in cases with old healed valves one (1.5 per

cent.), in secondary acute bacterial one (2 per cent.), in primary acute bacterial two (12 per cent.), and in the acute rheumatic it did not occur at all.

Forty-eight (67 per cent.) of subacute bacterial, fourteen (22 per cent.) of the cases with defective valves, sixteen (37 per cent.) of the secondary acute bacterial, ten (59 per cent.) of the primary acute bacterial, and only one (11 per cent.) of the acute rheumatic showed embolic processes in one or more forms. Only the subacute bacterial class contained a case having all four manifestations of emboli at the same time. The cases having infarction in both the spleen and kidneys are as follows: subacute bacterial fourteen (19 per cent.), cases with defective valves six (9 per cent.), secondary acute bacterial nine (21 per cent.), primary acute bacterial six (35 per cent.). This condition did not occur in the acute rheumatic hearts. Leaving out the petechiae as a consideration, since they may be caused by a variety of conditions other than embolic processes, on the basis of infarction of the spleen and kidneys and cerebral embolism, it is seen that forty-five (62 per cent.) of the subacute bacterial, twelve (19 per cent.) of those with defective valves, sixteen (37 per cent.) of the secondary acute bacterial, nine (53 per cent.) of the primary acute bacterial, and none of the acute rheumatic showed the presence of arterial embolism. When the total number of possible embolic processes, not including embolic glomerulonephritis, is noted, the various classes show the following number: subacute bacterial 105 (36 per cent.), cases with defective valves 21 (8 per cent.), secondary acute bacterial twenty-eight (16 per cent.), primary acute bacterial nineteen (28 per cent.), and acute rheumatic one (3 per cent.).

The presence of embolic processes in the cases of old healed defective valves is probably to be explained as a result of a previous bacterial endocarditis. Most of such infarcts are old. The following case is one of the 220 cases which illustrate this condition:

A white man, aged 37, admitted to the hospital on April 29, 1912, complained of weakness, shortness of breath, pain in the precordium and back. He stated that he had never had venereal diseases, scarlet fever, measles, diphtheria, tonsillitis or rheumatism. His trouble began about fourteen years before with a dull pain in the region of the heart, weakness and shortness of breath. He had no edema at that time. Symptoms remained about the same until he became much worse four years previous to his coming to the hospital. During an attack which lasted about five months, anasarca and ascites were present. At necropsy, edema was present in the feet. The peritoneal cavity contained about 200 c.c. of a yellow fluid. The right pleural cavity contained a large amount of yellowish fluid. The pericardial cavity was greatly distended with a straw colored fluid. The heart weighed 660 gm. Whitish patches were noted in the endocardium in the right auricle. The mitral leaflets were fused, thickened and calcified, giving the fish mouth appearance. Several large deep reddish nodules were present immediately under the pleura of the right lung. On section these were found to be red and triangular in shape. The spleen weighed 270 gm. The

cut surface showed a whitish area, triangular in shape, with the base toward the surface. This area was from 4 to 5 cm. wide and sharply demarcated. The liver weighed 2,300 gm. and showed passive congestion. On the surface of both kidneys were deep depressions which on section showed the cortexes replaced by masses of connective tissue sharply marked off from the surrounding cortex. Here there is no history of rheumatism. Old healed infarcts were present in both spleen and kidneys. The case strongly suggests a previous attack of bacterial endocarditis as the cause of defective valves.

It can be said in general that embolic processes have the highest incidence in subacute bacterial endocarditis, high in acute bacterial endocarditis, relatively low in cases with healed defective valves, and absent in the acute rheumatic cases. Abscesses when present as a result of infected emboli are associated with the acute forms. Anatomically, the presence of embolic processes seems to differentiate the active forms, subacute and acute bacterial, from the rheumatic. In cases of old healed defective valves, the presence of embolic processes, when we consider their absence in acute rheumatic cases, seems to indicate that healing of cases of primary or secondary acute bacterial or subacute bacterial endocarditis plays a rôle in the development of defective valves. The higher incidence of embolic processes in subacute bacterial endocarditis than in the acute, primary or secondary, might be accounted for by the fact that the vegetations have been present over a longer period of time and that the possibility of parts of the vegetations breaking off and causing a cerebral embolism or infarction of the spleen and kidneys is proportionately greater. The duration of the process should be considered in interpreting variations in findings in the acute and subacute bacterial forms of endocarditis. The presence of abscesses resulting from infected emboli is probably dependent on the virulence of the infective agent.

Embolic glomerulonephritis, as described by Loehlein [30] is common in subacute bacterial endocarditis. It is a condition, as pointed out by Baehr and Lande,[22] in which there is an infarction of parts of the glomerular tufts resulting from bacterial emboli dislodged from the infected heart valve. It occurs rarely or not at all in other classes. Baehr and Lande considered it characteristic of subacute bacterial endocarditis. They examined slides from several places in each kidney. In our cases, the determination was made from an examination of one or two blocks. Our findings can be considered conclusive only so far as they are positive. The relative frequency with which this condition occurs is interesting (Table 3). The percentage of case incidence is high in subacute bacterial endocarditis, thirty-five (55 per cent.); low in patients with old defective valves, two (4 per cent.); in primary acute endocarditis, two (12 per cent.), and in secondary acute, one

30. Loehlein: Med. Klin. **6**:375, 1910.

(2.5 per cent.). It is absent in the rheumatic cases. It is seen that this condition may be present in the old healed cases and in the acute forms in a few instances. In one of the two old healed cases infarction of the kidney was present. In neither case were bacteria found. In one of the two cases of primary acute bacterial endocarditis septic infarcts were present. Evidently, in rare cases both abscesses and embolic glomerulonephritis may occur at the same time. In the other primary case, no infarcts were present. In the secondary acute case *Streptococcus hemolyticus* was cultured from the blood. It should also be noticed that embolic glomerulonephritis does not occur in the same proportion in the subacute bacterial endocarditis as do the other embolic processes. This is accounted for probably by the degree of virulence of the organism in the bacterial emboli producing the embolic glomerulonephritis. Apparently only the less virulent strains produce embolic glomerulonephritis. The virulence of the organism is another factor always to keep in mind in interpreting processes associated with bacterial endocarditis.

SPLENIC ENLARGEMENT

Splenic enlargement is a usual finding in cases of subacute bacterial endocarditis. This has been emphasized by both clinicians and pathologists writing on the subject. Arnett,[31] in a study of splenic enlargement in 286 necropsies, found enlargement of the spleen in chronic passive congestion resulting from cardiac failure about one-half as frequent as in endocarditis. Starling,[20] in discussing the pathology of subacute bacterial endocarditis, reported enlarged spleens in sixteen of seventeen necropsies. Enlargement of the spleen can occur in any of the types of endocarditis, even to quite an extent in the acute rheumatic. The largest spleen found in our 220 cases was one weighing 1,400 gm. in a case of subacute bacterial endocarditis. The patient developed lobar pneumonia and at death *Streptococcus hemolyticus* was found in the blood. Considering the spleen weighing over 200 gm. as enlarged, enlargement is found in forty-five (62 per cent.) of the subacute bacterial cases, in twenty-seven (42 per cent.) of the cases with defective valves, in twenty-one (49 per cent.) of the secondary acute bacterial cases, in twelve (71 per cent.) of the acute bacterial cases, and in three (33 per cent.) of the acute rheumatic cases (Table 4). With spleens of this size, little difference is noticed in the frequency of its enlargement in the different classes. When 500 gm. or more are considered as enlarged, the enlargement is more frequent in the bacterial types. In subacute bacterial cases, such enlargement was found ten times (14 per cent.), in cases with old healed valves once (1.5 per cent),

31. Arnett, J. H.: Am. J. Med. Sc. **163**:590, 1922.

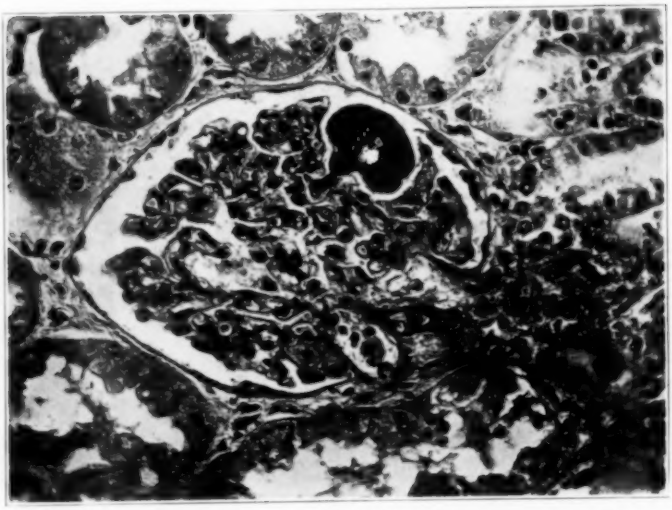

Fig. 1.—A clump of streptococci lodged in a glomerular tuft.

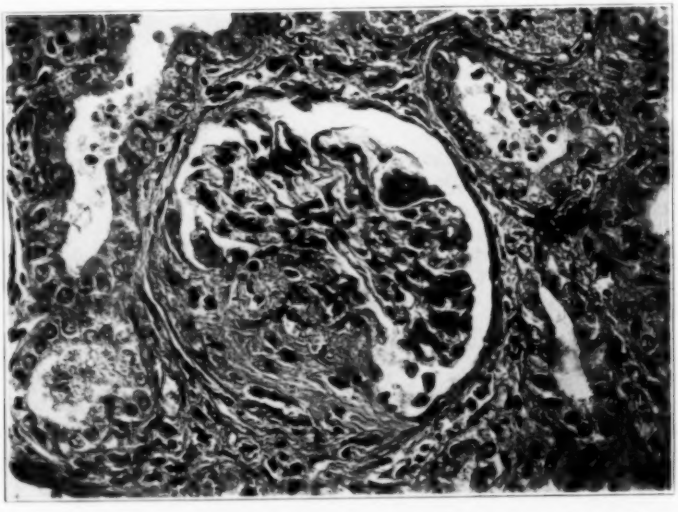

Fig. 2.—Embolic glomerulonephritis in a case of subacute bacterial endocarditis.

in the secondary acute bacterial five times (12 per cent.), in the acute bacterial twice (11.7 per cent.), and in the acute rheumatic not at all. Splenic enlargement is common in the subacute and acute bacterial forms and in the old healed valvular cases when enlargement not exceeding 500 gm. is considered, but when spleens weighing over 500 gm. are counted, the percentage in the bacterial forms is higher. It seems evident that splenic enlargement to the extent of being palpable would be much more common in bacterial endocarditis, acute or subacute, than in either the cases showing cardiac failure from defective valves or in the rheumatic cases. Marked enlargement of the spleen associated with cardiac disease results mainly from infection rather than from passive congestion. As in embolic processes splenic enlargement does not definitely separate subacute and acute bacterial cases of endocarditis, but it sets these off from the cases of acute rheumatic endocarditis.

TABLE 4.—*Enlarged Spleen*

Kind	200–250	250–300	300–350	350–400	400–450	450–500	Over 500	Percentage Over 500	Total	Total Percentage
Subacute bacterial endocarditis	9	9	11	4	1	1	10	14.0	45	62.5
Healed thickened valves	11	3	6	3	2	1	1	1.5	27	42.0
Secondary acute bacterial endocarditis	5	6	0	2	1	2	5	12.0	21	49.0
Acute bacterial endocarditis, independent	1	1	3	2	1	2	2	11.7	12	70.0
Acute rheumatic endocarditis	2	0	1	0	0	0	0	0.0	3	33.0

INVOLVEMENT OF THE ENDOCARDIUM

The vegetation itself, regardless of its location on the valve, has considerable significance, especially in differentiating the active bacterial forms from the rheumatic vegetations. Libman [26] describes the vegetations in the rheumatic hearts as being covered with endothelium, but Murray [27] found that the endothelium was not always present over the vegetations. Grossly, the vegetations in subacute bacterial endocarditis are usually large, pedunculated though sometimes sessile, villous and cauliflower-like. They are often soft, frequently calcified in parts, and often almost completely fill the orifices. Those in the primary and secondary bacterial cases, when examined grossly, are structurally similar to the subacute vegetations. Frequently they are smaller but not always. The acute forms, especially those of the secondary acute, are red, soft and velvety in appearance. While the vegetations of the subacute endocarditis cannot be differentiated grossly from the primary and secondary acute forms, all of these are decidedly different from those found in the rheumatic valves. In these the vegetations are

round or globular in shape, small (usually not more than from 2 to 5 mm. in diameter), smooth and glistening (Fig. 3). This explains why embolic processes are not present in such cases.

Microscopically, the vegetations in the subacute and the acute forms of bacterial endocarditis seem to be similar. They are essentially thrombi which are undergoing organization. They are usually covered with bacteria, practically always streptococci (Fig. 4). These, according to Libman,[32] prevent the endothelium from growing over the organized thrombus. The organization is conspicuous in being cellular and only slightly vascular. There is no difference apparently between

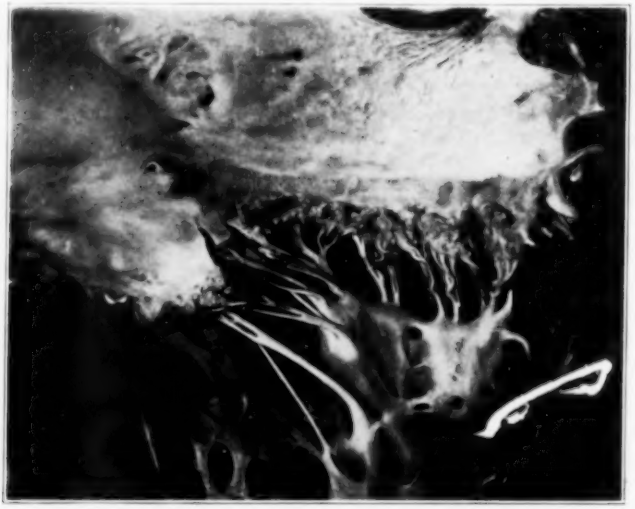

Fig. 3.—Vegetations in acute rheumatic endocarditis.

the active bacterial forms. Any of them may suppurate. The microscopic picture of the rheumatic vegetation is different. Baehr[33] describes the lesion as first being a proliferative inflammation over which the endothelial cells swell and desquamate. The denuded areas are covered with agglutinated blood platelets. The adjacent endothelium rapidly proliferates covering the surface of the blood platelet nodule and thus limiting the size. Later the verruca becomes organized and a ridgelike scar is formed. The lesion as shown in our section (Fig. 5) is present within the nodular vegetation, which is covered with endo-

32. Libman, E.: Characterization of Various Forms of Endocarditis, J. A. M. A. **80**:813 (March 24) 1923.
33. Baehr, G., cited by Libman.

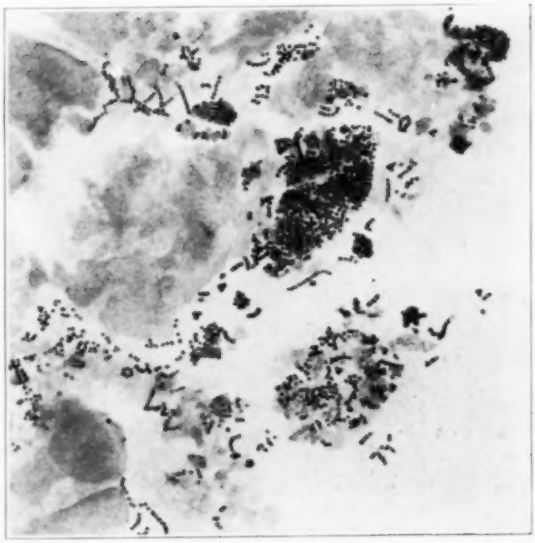

Fig. 4.—Vegetation of subacute bacterial endocarditis showing streptococci.

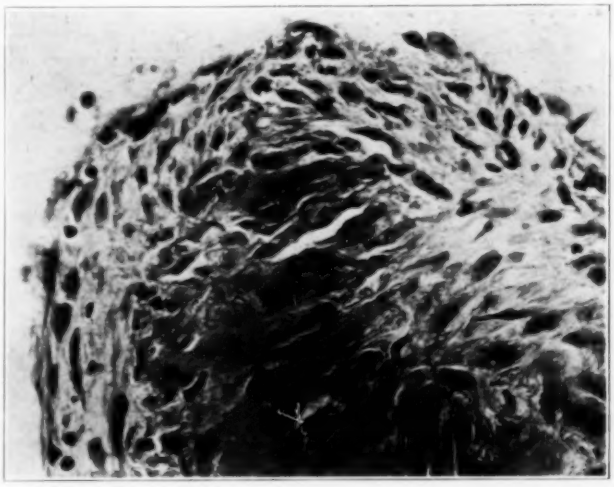

Fig. 5.—Rheumatic vegetation showing hyalinized area within the nodule.

thelium in many cases. There is little or no cellular exudate. The lesion is characterized by a hyalinized area (apparently hyalinized connective tissue) within the nodule, around which there is a marked proliferation. The reaction to the virus is characterized by proliferation rather than exudation. The endothelium may not cover the entire lesion, and the hyalinized material may extend beyond the endothelium, in this resembling the vegetation of the bacterial forms (Fig. 6). Whether the process is the same as the bacterial but slower, with rapid proliferation of connective tissue and endothelium, or whether it is strictly a proliferative process, is not entirely clear. Further work is

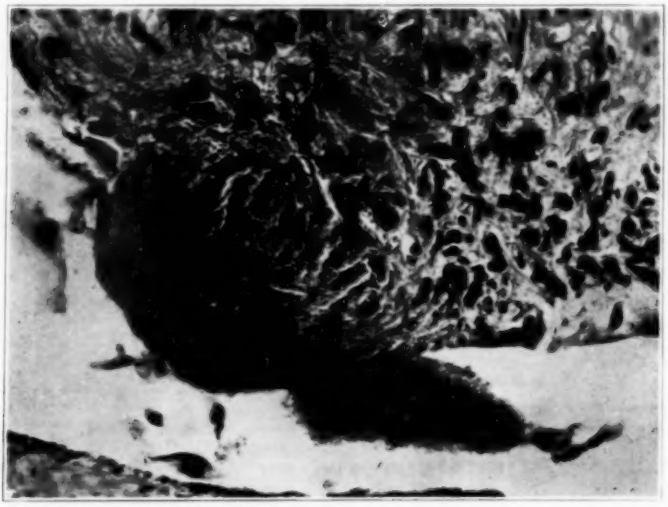

Fig. 6.—Rheumatic vegetation showing the hyalinized material extending beyond the endothelium.

being done to determine the process. In none of our rheumatic vegetations were bacteria found when stained, as were the bacterial vegetations, by the Gram-Weigert method. The vegetations of the subacute and primary and secondary acute bacterial endocarditis cannot be differentiated absolutely by either gross or microscopic examination, but they are easily differentiated from the type of vegetation found in the few hearts at our disposal, which were immediately associated with clinical cases of acute rheumatic fever. This decided difference between the bacterial and rheumatic types can apparently only be explained on the basis of the character of the lesion. A difference in virus is certainly strongly suggested.

The same heart may show lesions of rheumatic morphology on one valve and of bacterial morphology on another valve. This is especially seen in the following case.

A young white man, aged 23, admitted to the hospital on Nov. 8, 1920, complained of pain in the joints (hips, knees, ankles, shoulders, elbows and back) and shortness of breath. During his stay in the hospital he had a slight rise in temperature and a slight leukocytosis. Roentgen-ray examination showed the heart to be enlarged. On Dec. 1, 1920, he was discharged and on June 4, 1921, he was readmitted with a complaint of severe pain from hemorrhoids, dyspnea and some swelling of the ankles. At this time he again had a slight temperature and leukocytosis. He died on the date of admission, of cardiac failure. At necropsy edema was present in both legs. There was slight jaundice. About 200 c.c. of clear fluid were found in the peritoneal cavity. The heart was enlarged, weighing 575 gm. On the edges of the leaflets of the tricuspid valve were numerous small smooth round to globoid vegetations (rheumatic). The mitral valve was thickened, sclerotic and calcified, with a greatly narrowed orifice. On the surface of the thickened leaflets were numerous thick vegetations, some calcified and others pink and soft (bacterial). Both the spleen and kidneys were free from infarcts. The liver showed marked evidences of passive congestion.

TABLE 5.—*Involvement of Endocardium*

	Subacute Bacterial Endocarditis		Healed Thickened Valves		Secondary Acute Bacterial Endocarditis		Acute Bacterial Endocarditis, Independent		Acute Rheumatic Endocarditis	
	No.	%	No.	%	No.	%	No.	%	No.	%
Mitral	55	76	56	87.5	33	77	11	64	7	78
Aortic	34	47	40	62.5	14	33	8	41	6	67
Tricuspid	7	9.7	9	14	1	2.3	1	6	5	56
Mitral and aortic	19	26	27	42	3	7	1	6	0	0
Mitral, aortic and tricuspid	2	2.8	5	8	0	0	2	12	4	44
Auricle	11	15	0	0	0	0	0	0	0	0
Ventricle	16	22	0	0	3	7	0	0	0	0
Ulceration	19	26	0	0	2	5	3	17	0	0

The involvement of the auricular and ventricular endocardium associated with valvulitis has been reported as occurring only in subacute bacterial endocarditis. Horder [24] refers to this condition and thinks that failure of typical signs of valvular injury may be accounted for by the occurrence of the infection on the mural endocardium only. In our 220 hearts, the valves affected in order of frequency were the mitral, aortic and tricuspid (Table 5). In the subacute bacterial cases, the auricular endocardium was involved in eleven (15 per cent.) and the endocardium of the ventricle in sixteen (22 per cent.). The secondary acute bacterial cases showed no auricular involvement, but in three (7 per cent.) the ventricular endocardium was affected. Involvement of the mural endocardium is not found in the other classes. Anatomically the involvement of the mural endocardium is fairly characteristic of the subacute bacterial class, but may be present in the acute form. It is the strongest anatomic differentiation between subacute and acute bacterial forms. Perhaps the degree of difference could be

explained on the basis of the duration of the process so far as the acute and subacute bacterial forms are concerned, for in the longer duration of subacute bacterial endocarditis a greater possibility for spreading exists. This explanation does not hold with the rheumatic, for it may have a duration equal to that of subacute bacterial endocarditis.

The term ulcerative endocarditis has had a general use. To many the presence of embolic processes signifies the presence of ulcerated valves. If the breaking off of particles of vegetations is looked on as ulceration, it is common in the subacute and acute bacterial types, but if a destruction of valvular tissue or organized vegetations with sloughing is considered as ulceration, then it certainly is much less common. The latter condition is seen in Table 5 to be relatively rare, as it occurred in the subacute bacterial form nineteen times (26 per cent.), in the cases with old healed valves not at all, in the secondary acute bacterial cases twice (5 per cent.), in the primary acute bacterial cases three times (17 per cent.), and not at all in the acute rheumatic cases. Ulceration was present twenty-seven times (17 per cent.) in the 156 active cases of endocarditis, while embolic processes were present seventy-five times (48 per cent.). It is obvious that to produce embolic processes it is not necessary to have ulcerated valves. The term ulcerative endocarditis when used to indicate the presence of embolic processes is not good, for in most cases no ulceration actually occurs. Ulcerated valves cannot be used as a basis to differentiate subacute and acute bacterial forms. Its presence would rule out rheumatic endocarditis.

IMPLANTATION ON PREVIOUSLY INJURED VALVES

Most observers agree that hearts with valvular defects are more susceptible to reinfection than hearts with normal valves and that in a high percentage of cases of subacute bacterial endocarditis there is a history of a previous valvulitis which has apparently healed. Combs,[17] in a histologic examination of valves in subacute bacterial endocarditis, found that in most of the valves there had been a previous infection. In our seventy-two hearts grouping as subacute bacterial endocarditis, forty-one (57 per cent.) anatomically showed valves which were thickened to such an extent that a previous involvement was evident. Decided evidence of previous thickening was shown in eleven (25.5 per cent.) of the forty-three secondary acute bacterial cases, in twelve (71 per cent.) of the seventeen primary acute bacterial cases, and in two (22 per cent.) of the nine cases of the acute rheumatic hearts (Table 6). It seems apparent that the previously injured valve is less resistant to infection than the normal valve and that these valves are subject to infection in the acute bacterial and the rheumatic types as well as in the subacute bacterial. The condition is not specific of the subacute bacterial class.

PERICARDITIS

That rheumatic endocarditis is commonly associated with pericarditis and that in subacute bacterial endocarditis pericarditis is seldom found, was pointed out by Libman.[26] In our 220 hearts a study of the frequency in each class is made (Table 6). Pericarditis from the gross determination was found to occur as acute or healed with about the same frequency (18 to 19 per cent.) in all classes except in that of acute rheumatic hearts in which the percentage is very much higher (78 per cent.). Microscopic evidence of pericarditis showed it to be even more common. Pericarditis is not only more frequent in the rheumatic class, but the rheumatic virus seems also to be the most frequent causal agent in producing pericarditis in hearts with bacterial types of endocarditis or in hearts with defective valves. Rheumatism preceded or was present in nine (69 per cent.) of the thirteen cases of

TABLE 6.—*Relation of Rheumatism to Active Lesions, Old Healed Lesions, Pericarditis and Previously Thickened Valves*

	Subacute Bacterial Endocarditis		Healed Thickened Valves		Secondary Acute Bacterial Endocarditis		Acute Bacterial Endocarditis, Independent		Acute Rheumatic Endocarditis		Doubtful		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	Total
History of rheumatism....	36	50	19	29	6	14	5	29	9	100	5	33	80
Pericarditis.....	13	18	12	19	8	18.6	3	18	7	78	4	27	47
Previously thickened valve	41	57	..	..	11	25.5	12	71	2	22	7	47	73
Rheumatism with thickened valve.....	27	37.5* 66**	..	.	5	11.5* 45**	4	23.5* 33 *	1	11* 33**	2	13* 29**	39
Rheumatism with pericarditis.....	9	12.5* 69†	5	8* 42†	2	4* 25†	2	12* 67†	7	78* 100†	1	7* 25†	26

* Total percentage.
** Percentage of thickened valves preceded by rheumatism.
† Percentage of cases of pericarditis preceded by rheumatism; negative thirteen times.

pericarditis in the subacute bacterial class, in five (42 per cent.) of the twelve hearts with old defective valves, in two (25 per cent.) of the eight secondary acute bacterial, in two (67 per cent.) of the three acute bacterial, and in seven (100 per cent.) of the seven rheumatic hearts, or in twenty-six (55 per cent.) of the total forty-seven cases of pericarditis. This seems to show that pericarditis is relatively infrequent in any but rheumatic hearts, except when rheumatism has preceded the attack of acute or subacute bacterial endocarditis and that in such conditions the rheumatic virus is generally responsible.

MYOCARDITIS

It has been stated that the myocardium is seldom involved in subacute bacterial endocarditis. Occasionally there is an interstitial exudate composed of large or small mononuclear cells. The acute forms are

reported as having polymorphonuclear cellular exudate which differentiates them from the subacute bacterial and rheumatic classes. In our series, the myocardium of fifty-four hearts with subacute bacterial endocarditis was examined (Table 7). Definite indications of inflammation were found in thirteen (24 per cent.). The character of the exudate was mononuclear in all but two, in which polymorphonuclear leukocytes were found. In one of these, streptococci were found in the blood and on the heart valve in large numbers. In the other, there was no bacterial record. Forty-nine hearts showing primary acute or secondary acute bacterial endocarditis were examined microscopically. Twelve (24.5 per cent.) of these showed exudative inflammation. Five were mononuclear and seven were polymorphonuclear in character. The myocardium has been reported to be involved in rheumatic endocarditis in a much higher percentage than in any of the other types. The type of inflammation is considered specific. Aschoff nodules containing mononuclear cells and multinuclear large cells are looked on as specific of rheumatic endocarditis. The myocardium of nine cases grouping clinically as rheumatic endocarditis was examined. In none of these was there a polymorphonuclear exudate. In nine (100 per cent.) inflammation was indicated by mononuclear exudate, and in eight of the nine Aschoff nodules were present.

ASCHOFF NODULES

These nodules are reported to be found in the myocardium of rheumatic hearts and not in hearts of bacterial endocarditis. An examination of 156 hearts which showed healed valves or in which there was active endocarditis was made (Table 7). Fifty-four of these were of the subacute class, and in six the Aschoff nodules were found. A girl, aged 11, gave no history of rheumatism but had a history of cardiac trouble which was preceded about two years by chorea. A second patient had two previous attacks of rheumatism, the first eleven years and the second six years before death. A third patient had an attack of rheumatism ten years before. A fourth patient gave a history of painful and swollen joints several months prior to the recent attack, and a fifth patient gave a history of painful joints about five months before death. In all of these cases, there was a history of rheumatism except in one, but in this one there was a thickened valve which suggests a previous rheumatic infection. The longest interval between the rheumatic attack and the final illness, ten years, occurred in the third case. Eleven other patients with subacute bacterial endocarditis with a previous history of rheumatism of ten years or less had no Aschoff nodules in their myocardium. In these there was no absolute evidence that the Aschoff nodules did not exist. They might have been found by examining slides from other parts of the heart.

Thirty-nine hearts with old healed valves were examined, and in three of these the Aschoff nodules were observed. In the first two cases there was no history of a previous attack of rheumatism. No embolic processes were found in these at necropsy. This might suggest that these thickened valves were produced by the rheumatic virus. In the third case, a history of rheumatism five years before was recorded. Here the Aschoff nodules seemed to have remained for a period of five years. Three other cases with defective valves and a previous history of rheumatism of five years or less did not show Aschoff nodules.

The hearts of seventeen primary acute and thirty-two secondary acute cases of bacterial endocarditis were observed, and in these forty-nine Aschoff nodules were found three times (Table 7). In the first, a history of rheumatism a short time before was mentioned. In the second, there was no history of rheumatism, but there was a previously thickened valve and no evidence of embolic processes. Two other acute

TABLE 7.—*Relation of Myocarditis to Endocarditis*

Kind	Number Examined	Myocarditis		Mononuclear Exudate	Polymorphonuclear Exudate	Aschoff Nodules	
		Number	Percentage			Number	Percentage
Subacute bacterial endocarditis	54	13	24	11	2	6	11
Healed thickened valves	39	6	15	6	0	3	7.7
Secondary acute bacterial endocarditis and acute bacterial endocarditis, independent	49	12	24.5	5	7	3	6
Acute rheumatic endocarditis	9	9	100	9	0	8	89

cases with a history of rheumatism of four years or less previous to death were examined, but no Aschoff nodules were found.

In eight of the nine rheumatic hearts Aschoff nodules were found. It is seen that in this type the percentage is much higher than in the other classes. The findings in this series seem to show that the myocardium is involved in a much higher percentage in the rheumatic hearts than in either the acute or subacute bacterial classes. The polymorphonuclear type of cellular exudate is most common in the acute bacterial forms, rare in the subacute bacterial, and not found at all in purely rheumatic carditis. The Aschoff nodules are characteristic of rheumatic carditis, and when they are found in other types there has been a previous rheumatic infection. These bodies may remain as long as ten years after infection, but on the other hand they apparently may disappear in much less time.

RHEUMATISM

The frequency of an attack of acute rheumatism previous to attacks of subacute bacterial endocarditis has been emphasized by many writers. It has been thought the chief cause of previously thickened valves on

which fresh vegetations commonly develop. Libman [26] emphasized the fact that rheumatic endocarditis may be acute, recurrent or chronic. It is a common finding to have one attack of rheumatism follow another. Just how a rheumatic valve progresses to extreme thickening and deformity is not entirely clear, but in some cases at least it seems to be through recurrent or continuous infections with the rheumatic virus. The following case in our series seems to show this continuous process. The patient died when the process was still in progress.

A white girl, aged 14, was first admitted to the hospital on April 9, 1912, with cardiac trouble. She had acute rheumatic arthritis when 9 years of age. She remained in the hospital until May 1, 1912. She improved and was discharged with a diagnosis of mitral stenosis. In June, 1913, she had a severe attack of tonsillitis. The cardiac condition immediately became worse, and she suffered from rheumatic pains in the fingers. She was readmitted to the hospital on July 15, 1913. The tonsils were enlarged and inflamed. There were subcutaneous rheumatic nodules on the fingers. During the first week in August she developed chorea, which ran a severe course. On Sept. 16, 1913, after a tonsillectomy, she became irrational. On Sept. 22, 1913, she became unconscious. The next day her temperature rose from 98 to 104 F. She died on Sept. 26, 1913.

At necropsy no edema was noted. The pericardial cavity was completely obliterated by fibrous adhesions. The heart was greatly enlarged. The leaflets of the tricuspid valve were thickened. On the ventral surface near the margins of the leaflets were numerous small globoid vegetations. The mitral orifice was distinctly narrowed. The leaflets of the mitral valve were thickened and showed numerous similar globoid nodules. No indications of infarction were found in the spleen or kidneys. The liver showed passive hyperemia. In this case there were thickened valves on top of which were active rheumatic vegetations. From the history it would seem that the thickened valves were caused by the rheumatic virus.

In our cases, a history in which rheumatism was mentioned occurred ninety-three times (Table 6). Eighty (36 per cent.) of these gave a positive history of rheumatic fever and thirteen a negative history. The number of positive cases of rheumatism is probably greater than the recorded cases show. In comparing the different classes, it is seen that, aside from the acute rheumatic class itself, the subacute bacterial class shows the highest case incidence of a previous attack of rheumatism. In seventy-two cases of subacute bacterial endocarditis a previous attack of rheumatism occurred in thirty-six (50 per cent.). A previous history of rheumatism was present in nineteen (29 per cent.) of the cases of old healed valves, in six (14 per cent.) of the cases of secondary acute bacterial endocarditis and in five (29 per cent.) of the acute bacterial class.

Previously thickened valves are probably produced by the rheumatic virus in more cases than by any other infective agent. Of the forty-one previously thickened valves in the subacute bacterial cases, twenty-seven (66 per cent.) were preceded by an attack of rheumatism. A previous attack of rheumatism was present in the other classes with previously

thickened valves as follows: Five (45 per cent.) of the eleven secondary acute bacterial, four (33 per cent.) of the twelve acute bacterial, and one (33 per cent.) of the three rheumatic hearts.

These findings show that a previous rheumatic infection is frequent in cases of endocarditis, especially in the subacute bacterial types. They also indicate that rheumatism plays an important rôle in producing thickening of the valve leaflets in both the old healed valve group and in the cases of subacute bacterial endocarditis with previously thickened valves.

BACTERIOLOGY

Horder [24] says he thinks that bacteria are present in the blood and on the valves throughout the course of the disease in subacute bacterial endocarditis, but Libman [26] is of the opinion that there may be a bacteria-free stage. In Gow's [19] opinion the finding of the organism in the blood stream is of great diagnostic importance, but conversely he considers the failure to find the organism of little importance. Boyd [15] found that streptococci may be adhering to the cusps when the blood stream is free. All have found that *Streptococcus viridans* is the chief organism in the subacute bacterial endocarditis and that the acute bacterial endocarditis is produced generally by *Streptococcus hemolyticus*, staphylococcus and pneumococcus. It is believed by most workers that rheumatic endocarditis results from an unknown virus, but Poynton [14] says he feels certain, on the other hand, that this type too is produced by *Streptococcus viridans*. Combs [17] suspects that rheumatic endocarditis may be produced by *Streptococcus viridans* and the anatomic difference may be a result of different degrees of resistance on the part of the host. Murray [27] obtained a lower percentage of *Streptococcus viridans* (80 per cent.) than Libman [26] in the subacute bacterial class, and in one series he and Lougheed [21] recorded finding sixty-six per cent. of *Streptococcus hemolyticus* in cases of endocarditis resembling subacute bacterial endocarditis. Curschman [34] reported twelve cases of subacute bacterial endocarditis in five of which *Streptococcus hemolyticus* was found. Combs [17] believes the infecting organism is comparatively unimportant and is not constant. Horder [24] stresses the fact that the organism producing subacute bacterial endocarditis is one of low virulence. This we find important in considering why certain strains produce a definite type of endocarditis. Both Libman [22] and Kinsella [35] found that the blood of patients having subacute bacterial endocarditis had agglutinins and complement-fixing bodies for homologous strains of nonhemolytic streptococci isolated from the blood. They

34. Curschman: München. med. Wchnschr. **69**:419, 1922.
35. Kinsella, R. A.: Streptococcus Endocarditis, Arch. Int. Med. **19**:367 (March) 1917.

found that this was not true in cases of rheumatic endocarditis in which streptococci were found in the blood. Kinsella found no biologic or immunologic constancy between strains isolated from different cases of subacute bacterial endocarditis.

In our 220 cases, there are only seventy-one in which there is a bacteriologic report (Table 8). In forty-six of these, positive bacteriologic findings are given. A negative report is given in twenty-five. Thirty of the seventy-one cases reported are classified as subacute bacterial endocarditis, and positive findings were obtained in twenty-two. *Streptococcus viridans* was found ten times, *Streptococcus hemolyticus* eight times, the staphylococcus twice, and the pneumoccus once. While this might suggest that *Streptococcus hemolyticus* frequently produces subacute bacterial endocarditis, it is necessary to take into consideration that in every case but one the organism was isolated from the heart blood at necropsy. It has been our experience

TABLE 8.—*Bacteriology*

Kind	Cases Reported	Positive Findings	Negative Findings	Viridans	Hemolyticus	Staphylococcus	Pneumococcus	Streptococcus
Subacute bacterial endocarditis	30	22	8	10	8	2	1	1
Healed thickened valves	13	4	9	1	2	1	0	0
Secondary acute bacterial endocarditis	17	14	3	2	6	3	3	0
Acute bacterial endocarditis, independent	6	4	2	0	3	1	0	0
Acute rheumatic endocarditis	5	2	3	1*	0	0	1	0
Total	71	46	25	14	19	7	5	1

* Pericardial fluid.

that the frequency of *Streptococcus hemolyticus* as an agonal invader is much greater than that of *Streptococcus viridans*. The one case with antemortem findings gave a history of middle ear infection previous to the heart trouble. Four of the thirteen cases of hearts with old healed valves gave positive bacterial findings in a blood culture. One contained *Streptococcus viridans*, two *Streptococcus hemolyticus* and one *Staphylococcus aureus*. In the primary and secondary acute forms, *Streptococcus hemolyticus* was present more frequently. In the acute rheumatic forms, *Streptococcus viridans* was found once and the pneumococcus once. While our bacterial findings are not extensive enough to merit definite conclusions, it is suggested, as Murray and Curschman reported, that *Streptococcus hemolyticus* may not be an uncommon etiologic factor in producing the subacute bacterial endocarditis and that it is the usual organism producing the acute types. It is likely that the virulence of the organism rather than the kind determines the course that the vegetative endocarditis will take.

CAUSE OF DEATH

There seems to be a rather general agreement with Horder [24] that in the major part of the course of subacute bacterial endocarditis, cardiac symptoms are not conspicuous. He found death occurring from toxemia, from heart failure, from uremia or from cerebral or coronary embolism. While cardiac symptoms may not be common early in the course of the disease, at death evidences of cardiac failure are conspicuous findings. In this series evidence of cardiac failure, as manifested by edema in its various forms and passive congestion of the liver, is common (Table 9). In fifty-nine (82 per cent.) of the seventy-two cases of subacute bacterial endocarditis, edema was present (as edema seen externally) as hydrothorax, hypericardium or ascites. It was present in forty-seven (73 per cent.) of the cases with old healed valves, in sixteen (37 per cent.) of the secondary acute bacterial cases, in six (35 per cent.) of the acute bacterial cases and in four (44 per cent.) of

TABLE 9.—*Evidence of Cardiac Failure*

	Subacute Bacterial Endocarditis		Healed Thickened Valves		Secondary Acute Bacterial Endocarditis		Acute Bacterial Endocarditis, Independent		Acute Rheumatic Endocarditis	
	No.	%	No.	%	No.	%	No.	%	No.	%
Edema	59	82	47	73	16	37	6	35	4	44
Passive hyperemia of the liver	65	90	58	91	25	58	13	76.5	9	100

the cases of acute rheumatic endocarditis. The lowest incidence is found in acute cases. Passive hyperemia of the liver was present in a higher percentage in all the classes than was edema. Infarction of the lungs was not an uncommon finding.

Various causes of death were evident in the subacute bacterial class as cardiac failure, sepsis, cerebral embolism, bronchopneumonia and lobar pneumonia, but by far the most frequent cause was cardiac failure. This condition was not infrequently complicated with other causes. In the cases with old healed valves the only cause of death worthy of note was cardiac failure. In the secondary acute bacterial cases the causes were more varied, as cardiac failure, sepsis, accident, miliary tuberculosis, carcinoma of different parts, bronchopneumonia and lobar pneumonia, starvation, chronic pulmonary tuberculosis, peritonitis, pericarditis, acute poliomyelitis, pernicious anemia, diabetes, myelogenous leukemia and Addison's disease. Chief among these causes is sepsis. In the acute bacterial class, as in the subacute bacterial, cardiac failure as a cause of death predominated. Cardiac failure and pericarditis rank as the chief causes of death in cases of acute rheumatic endo-

carditis. It is obvious that, while various conditions produce death in endocarditis, cardiac failure is the common condition which directly or indirectly results in death.

In the analysis of these 220 hearts, two main conditions are met: the actively inflamed valves and the healed thickened valves with their associated pathology. The active progressive cases may be placed in two groups which apparently are differentiated by practically all tests applied. The first is the simple or verrucous endocarditis (rheumatic endocarditis), and the second, with the more villous lesion of the valves, might be included in the term bacterial endocarditis. These two forms not only differ pathologically, but they also seem to be separated clinically. The former is practically always associated with acute rheumatic fever or chorea and occurs as a primary infection rather early in life. It is characterized by small, rounded and smooth vegetations which are apparently a result of proliferative inflammation. Bacteria are not found in the vegetations. In practically all cases there is an immediate association with pericarditis and myocarditis. In the latter a special form of inflammatory reaction (Aschoff nodules) is practically always found. Embolic processes, because of the firmness of the vegetations, do not occur. The lesions are confined to the valvular endocardium. The valves, once injured, become more susceptible to reinfection with the same virus or with bacteria, usually streptococci. The spleen may be moderately enlarged. This type is seldom fatal at the time of the active process. In the few cases in which it does prove fatal the causes of death are usually cardiac failure and pericarditis. It is the usual cause of the thickened healed valves which later in life commonly result in death from cardiac decompensation. Not infrequently the healing of bacterial endocarditis leaves a deformed thickened valve.

The second group cannot be divided into subgroups as easily pathologically as it can clinically. Its vegetations are large, friable, generally filled with bacteria and tend to spread to the mural endocardium, depending on the duration of the process. Myocarditis and pericarditis are rarely associated with this group. Embolic processes are common. Embolic glomerulonephritis occurs in cases with a slow process. Previous attacks of rheumatism with rheumatic endocarditis greatly predispose to this form. Death usually results from cardiac failure. Since bacteria are generally found in the blood and on the valves, it seems advisable to use the etiologic basis for classification and call this form bacterial endocarditis. The clinical terms acute and subacute bacterial endocarditis are valuable, for they include the duration and the etiology, the chief factors concerned in interpreting endocarditis. The acute bacterial form may further be divided into primary and secondary acute endocarditis depending on whether it develops independently or as a result of some definite focus of infection. Since ulcera-

tion of the valves is not common, the term ulcerative endocarditis is misleading. It would seem that the clinical terms subacute and acute bacterial endocarditis would be the most useful for the present, until the etiology of rheumatic endocarditis is definitely established. The terms endocarditis lenta and slow endocarditis have a clinical significance and a meaning similar to subacute bacterial endocarditis. Confusion may be avoided by using the term endocarditis for the active processes and defective valves for the healed processes.

CONCLUSIONS

Death occurring from cardiac failure before the age of 40 is practically always a result of valvular injury. The injury may be an acute process or a healed thickened condition resulting from a previous valvulitis.

Endocarditis associated immediately with acute rheumatism (rheumatic endocarditis) seldom causes immediate death. When in rare cases death does occur, it usually results from pericarditis and cardiac failure.

Embolic processes are common in all forms of bacterial endocarditis. These processes are most frequent in the subacute bacterial form. This probably can be accounted for by the longer duration. Embolic processes do not seem to occur in acute rheumatic endocarditis.

Embolic glomerulonephritis is rarely found in any form of endocarditis except in subacute bacterial endocarditis in which it occurs in a high percentage of cases. Its occurrence seems to bear no direct relationship to other forms of embolic processes. The chief factor determining its presence seems to be the presence of organisms of low virulence on the heart valves. *Streptococcus viridans* is the usual organism, but the condition may be produced by *Streptococcus hemolyticus*.

The presence of embolic processes in cases with healed defective valves suggests that bacterial forms of endocarditis not infrequently heal, since in rheumatic endocarditis embolic processes are not found.

Splenic enlargement (to the extent of being palpable) associated with cardiac trouble generally indicates an active inflammatory condition of the valves rather than an enlargement from passive congestion.

The vegetations in acute and subacute bacterial endocarditis cannot be differentiated. They are essentially thrombi. The rheumatic vegetations are easily differentiated from the bacterial. They seem to be a condition resulting from a proliferative type of inflammation.

The active involvement of the auricular and ventricular endocardium rarely occurs except in subacute bacterial endocarditis. This is probably accounted for by the longer duration of the process in the subacute form.

Valvular ulceration is not a common finding. It occurs most frequently in the subacute bacterial class. Apparently it never occurs in rheumatic endocarditis. The term ulcerative endocarditis should not be used to indicate the presence of embolic processes, for the presence of embolic processes bears no direct relationship to ulcerated valves.

Previously injured valves are apparently more susceptible to infection than normal valves. In most cases they seem to have resulted from rheumatic infection, often recurrent and chronic, but they may be produced by the healing of bacterial infected valves.

Pericarditis is generally present in rheumatic endocarditis. It is seldom found in bacterial endocarditis not preceded by a rheumatic infection.

Myocarditis is practically always associated with rheumatic endocarditis but seldom occurs in the bacterial forms.

The presence of Aschoff nodules is apparently specific of a rheumatic infection. They may be found in the myocardium of cases with active bacterial valvulitis or in cases with healed defective valves when there has been a fairly recent previous attack of rheumatic carditis.

A rheumatic infection commonly precedes subacute bacterial endocarditis and is not infrequent in the other forms.

The finding of *Streptococcus viridans* in the blood in a case of endocarditis indicates a subacute bacterial form. The presence of *Streptococcus hemolyticus* or staphylococcus generally indicates an acute form of bacterial endocarditis, but by no means rules out the subacute form.

Whether a case of bacterial endocarditis will take an acute or subacute course depends on the virulence of the organism rather than on the kind.

The chief cause of death in endocarditis is cardiac decompensation.

Apparently the two main factors to keep in mind in interpreting variations in the findings in bacterial endocarditis are the duration of the process and the virulence of the organism producing the lesion. The former seems to be dependent on the latter.

THE EFFECT OF CERTAIN PAST DISEASES ON VITAL CAPACITY *

W. P. SHEPARD, B.S., M.D.

MINNEAPOLIS

In seeking normal standards on which to base vital capacity readings, practically all investigators have found a considerable percentage of unexplained low readings in persons supposed to be normal. That there is a decided variation in the lung capacity of normal persons cannot be questioned, though recent work has tended to reduce this variation by corrections for age, sex, weight, height, surface area, chest circumference, sitting height, etc. In going over the vital capacity records recently of 1,304 male university students selected at random, we [1] pointed out that many of the low readings could be accounted for on the basis of past or present diseases. The present study was undertaken with a view to noting the effect of certain past intrathoracic diseases on the vital capacity. Few, if any, of the series reported heretofore have been correlated with as complete a history and physical examination as was available in the series here reported.

The Student's Health Service records of 1,517 male students comprising the freshman class entering the University of Minnesota in the fall of 1922 were available. The histories of these men were taken by medical students who filled out uniform blanks at the time of the entrance physical examinations. The examinations were conducted by the combined staffs of the health service and physical education department (fifteen physicians and twelve nurses), augmented by sufficient medical students and clerks to do the routine recording. Those students giving histories of epidemic influenza, pneumonia, pleurisy, pulmonary tuberculosis or heart disease, and those who at the subsequent examination showed physical signs of pleurisy, tuberculosis or organic heart disease, were selected for special study. Vital capacity readings were taken on all of the 1,517 students with a Sanborn water spirometer, a nurse and medical student especially instructed in the use of the machine being detailed to procure readings. Ample time was allowed each student to have the machine explained and to be given a minimum of three trials, the highest being recorded as his vital capacity. Standing height and

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* From the Student's Health Service and Department of Preventive Medicine and Public Health, Medical School, University of Minnesota.

* Read before the combined Lymanhurst and Parkview Sanatorium staffs, June 26, 1923.

1. Shepard, W. P., and Myers, J. A.: Journal-Lancet **43**:14, 355 (July 15) 1923.

weight were measured with students stripped. Sitting height was taken according to the method of Dreyer,[2] with the students stripped. Chest circumference was measured at the level of the fourth rib on deep inspiration and deep expiration, and the computed mean was used as recommended by Parmenter and Gray.[3] Surface area was computed from the height and weight according to the formulas of Du Bois and Du Bois.[4] With these basic data, the vital capacity was reckoned in percentage of normal by the use of the tables of Myers,[5] and a determination obtained according to: (1) weight, (2) sitting height, (3) surface area and (4) chest circumference. These four determinations were then averaged and this figure taken as the person's vital capacity in percentage of normal.

Curves used in the figures for the usual distribution of vital capacities for male students were computed from the present series of

TABLE 1.—*Distribution of Vital Capacity in Diseases Studied*

Percentage Normal Vital Capacity	Epidemic Influenza		Pneumonia		Pleurisy		Tuberculosis		Cardiac	
	Cases	Per Cent.	Cases	Per Cent.	Cases	Per Cent.	Cases	Per Cent.	Cases	Per Cent.
Under 70	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
71 to 75	2	0.6	1	0.5	0	0.0	2	10.0	0	0.0
76 to 80	7	2.1	6	3.2	3	5.4	2	10.0	0	0.0
81 to 85	8	2.4	8	4.2	6	10.0	1	5.0	1	7.1
86 to 90	18	5.4	14	7.4	8	14.5	5	25.0	3	21.4
91 to 95	48	14.4	26	13.8	12	21.8	4	20.0	1	7.1
96 to 100	62	18.6	41	21.7	7	12.7	2	10.0	0	0.0
101 to 105	67	20.1	31	16.4	6	10.9	1	5.0	2	14.3
106 to 110	36	10.8	31	16.4	6	10.9	0	0.0	3	21.4
111 to 115	44	13.2	17	8.9	2	3.6	1	5.0	4	28.6
116 to 120	26	7.8	9	4.8	4	7.3	2	10.0	0	0.0
Over 120	15	4.5	5	2.6	1	1.9	0	0.0	0	0.0
Totals....	333	99.9	189	99.9	55	99.9	20	100.0	14	99.9

1,517 and the previous series of 1,304, a total of 2,821. These vary slightly from the distribution reported by Hewlett and Jackson [6] and Myers and Myers [7] for male college students.

In each disease studied the distribution of vital capacities in both number of cases and percentage is shown in Table 1. The percentage of normal vital capacity in the first column is the average of the four determinations as described above. The number of cases under each

2. Dreyer, J., and Hanson, J. F.: The Assessment of Physical Fitness, New York, Paul B. Hoeber, 1921.

3. Parmenter, D. C., and Gray, Horace: Chest Measurement as a Gage of Body Weight, J. A. M. A. **79**:26; 2159 (Dec. 23) 1922.

4. Du Bois, D., and Du Bois, E. F.: A Formula to Estimate Approximate Surface Area if Height and Weight Be Known, Arch. Int. Med. **17**:863 (June) 1916.

5. Myers, J. A.: A Method for Quickly Obtaining the Percentage of an Individual's Theoretical Normal Vital Capacity of the Lungs, Am. Rev. Tuberculosis **7**:161 (May) 1923.

6. Hewlett, A. W., and Jackson, N. R.: The Vital Capacity in a Group of College Students, Arch. Int. Med. **29**:515 (April) 1922.

7. Myers, J. A., and Myers, Frank J.: Journal-Lancet **43**:276 (June 1) 1923.

heading having vital capacities from 81 to 85 per cent. of normal, 86 to 90 per cent., 91 to 95 per cent., etc., is listed opposite the appropriate heading. The incidence percentage of the various vital capacities is then shown in the column beside the number of cases.

A curve is prepared for each of the diseases studied on which the normal distribution of vital capacities computed from a total of 2,821 male students is shown in a heavy black line. Superimposed on this curve is the distribution of vital capacities in the particular disease group under consideration, shown by a light black line. The ordinate in each figure represents the incidence percentage of the various vital capacities, as shown in Table 1. The abscissa in each figure represents the vital capacities averaged and expressed in percentage of normal, as shown in the first column of Table 1. With this arrangement, it will be seen that any agent tending to diminish vital capacity will result in a lowering of the height of the distribution curve and in a shifting of the curve to the left. To illustrate the relative amounts of reduction in each of these diseases, the areas between curves are shaded whenever the disease curve is either lowered or shifted to the left. Roughly, then, the amount of reduction of vital capacity in a group of students giving histories of influenza, pneumonia, pleurisy, etc., may be estimated by the size of the area which is shaded.

INFLUENZA

In view of the frequency of pulmonary complications incident to the epidemic influenza of 1918 and 1919, and since many of these patients were unable to procure adequate medical attention and did not know whether or not pneumonia developed, this group was included for study. Only those who gave a history of influenza between 1917 and 1920 were considered. These numbered 333 cases out of the total of 1,517. The vital capacities of this group are listed in Table 1 and compared to the normal distribution in Chart 1. It will be seen that there is a slight lowering and shifting to the left of the influenza curve, indicating a slight reduction in vital capacity in the group as a whole. The significance of so slight a reduction may well be questioned as being within the limits of error of the method employed.

PNEUMONIA

There were 189 students who gave histories of pneumonia. Unfortunately, no differentiation could be made between lobar pneumonia and bronchopneumonia, and nothing was known of the severity of the disease. The age of the person at the time of the attack was given in each case. The vital capacities of this group are listed in Table 1 and illustrated in comparison to the normal in Chart 2. Here again, there

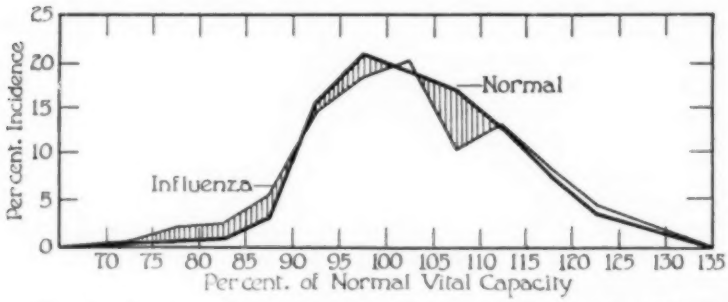

Chart 1.—Remaining effect of epidemic influenza on vital capacity (333 cases).

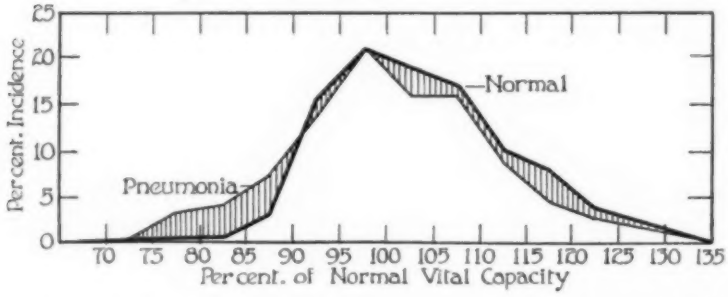

Chart 2.—Remaining effect of pneumonia on vital capacity (189 cases).

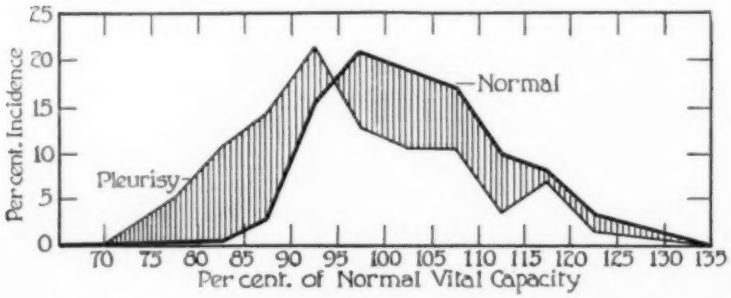

Chart 3.—Remaining effect of pleurisy on vital capacity (fifty-five cases).

is a slight but definite lowering of the curve and a shifting to the left, a little more marked in this group than in the influenza series. The size of the shaded area is somewhat increased in this over that of the influenza figure. Here, again, the reduction is so slight as to be of questionable significance.

Recent studies by Stewart and Sheets,[8] Wilson and Edwards[9] and Emerson and Green[10] have attracted attention to the vital capacities of children in health and disease. Apparently no special study was made of pneumonia. Several students in the present series were observed who had a low vital capacity without demonstrable cause even after repeated physical examinations over a period of several months. The only factor common to all these students was that they had had severe pneumonia at ages below 5 years. For this reason this entire group was analyzed from the standpoint of age at which pneumonia was contracted.

TABLE 2.—*Effect of Age When Person Had Pneumonia on Vital Capacity*

	Total Cases	Cases Below 90% of Normal	Percentage Below Normal
Pneumonia under age 2	29	5	17.2
Pneumonia between ages of 2 to 5	44	2	4.5
Pneumonia between ages of 5 to 10	49	8	16.6
Pneumonia between ages of 10 to 20	67	10	15.0

Results are shown in Table 2 in which it is seen that there is apparently a slight increase in the number of low vital capacity readings when pneumonia was contracted at earlier ages, but the difference is slight.

PLEURISY

In considering pleurisy, only those who gave definite histories of severe attacks or repeated mild attacks, or those who showed physical signs of pleurisy on physical examination were considered. These numbered fifty-five out of the total of 1,517. The vital capacities are listed in Table 1 and illustrated in comparison to the normal in Chart 3. This is the first figure that shows a definite reduction in vital capacity of the group as a whole. There is a marked lowering of the height of the curve and a shifting to the left. The shaded area is considerably increased over that in the preceding two charts.

8. Stewart, C. A., and Sheets, O. B.: The Value of the Determination of Vital Capacity of the Lungs in the Diagnosis and Prognosis of Pulmonary Tuberculosis in Children, Journal-Lancet **42**:253 (May 15) 1922. Stewart, C. A.: The Vital Capacity of the Lungs of Children in Health and Disease, Am. J. Dis. Child. **24**:451 (Dec.) 1922.

9. Wilson, May J., and Edwards, D. J.: Standards for Normal Vital Capacity for Children; the Lung Capacity in Certain Intrathoracic Conditions, Am. J. Dis. Child. **22**:443 (May) 1921.

10. Emerson, P. W., and Green, H.: Vital Capacity of the Lungs of Children, Am. J. Dis. Child. **22**:202 (March) 1921.

TUBERCULOSIS

Only cases in which there was a history of a diagnosis of tuberculosis together with prolonged sanatorium treatment or in which there were physical signs together with a history of a previous diagnosis were considered. Twenty such cases were found. The lung capacities are recorded in Table 1 and illustrated in Chart 4. So far as could be determined by entrance examination and subsequent observation, all cases were arrested. While the total number is small, the curve indicated a marked reduction in lung capacity of the group as a whole. These findings are in accord with those of Dreyer,[11] Myers,[12] Wilson and Edwards,[9] Stewart and Sheets,[8] all of whom find a reduction in vital capacity in tuberculosis.

HEART DISEASE

Only those persons who gave a history of heart disease with decompensation or who showed definite physical signs of organic disease together with some impairment of their physical condition were considered. The total was fourteen cases. Here again the series is small, but there is a definite lowering of vital capacity, as shown in Table 1 and Chart 5. All cases were apparently compensated at the time of examination and through six months' subsequent observation. This is contributory to the findings of Lattimore,[13] Ulrich and Nathanson,[14] who have studied vital capacity in various cardiac conditions.

CONCLUSIONS

1. Vital capacity is studied in 611 male university students who gave histories of influenza, pneumonia, pleurisy, pulmonary tuberculosis or heart disease. These are compared to vital capacity readings in 2,821 male students.

2. Each person's vital capacity is computed by averaging four determinations, namely: weight, sitting height, surface area and chest circumference. The result is expressed as percentage of normal.

3. Influenza and pneumonia appear to lower the vital capacity of a large group, although the change is slight.

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11. Dreyer, G., and Burrell, L. S. T.: Vital Capacity Constants Applied to Pulmonary Tuberculosis, Lancet **2**:374 (Aug.) 1922.

12. Myers, J. A.: A Comparison of Vital Capacity Readings and X-Ray Findings in Pulmonary Tuberculosis, Tr. 17th Annual Meeting of National Tuberculosis Assn., 1922, p. 136.

13. Lattimore, Ralston: Vital Capacity Readings, Tr. Med. Assn. of Georgia, 74th Annual Meeting, May, 1923; abstr., J. A. M. A. **80**:1540 (May 26) 1923.

14. Ulrich, H. L., and Nathanson, M. H.: The Vital Capacity of the Lungs in Cardiac Disease, Minnesota Med. **4**:721 (Dec.) 1921; The Vital Capacity of the Lungs in Cardiac Disease, to be published.

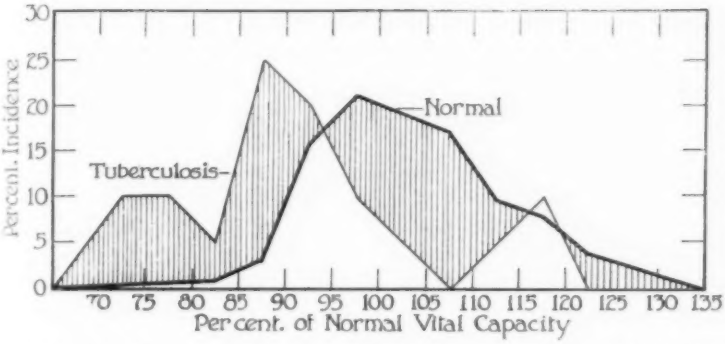

Chart 4.—Remaining effect of pulmonary tuberculosis on vital capacity (twenty cases).

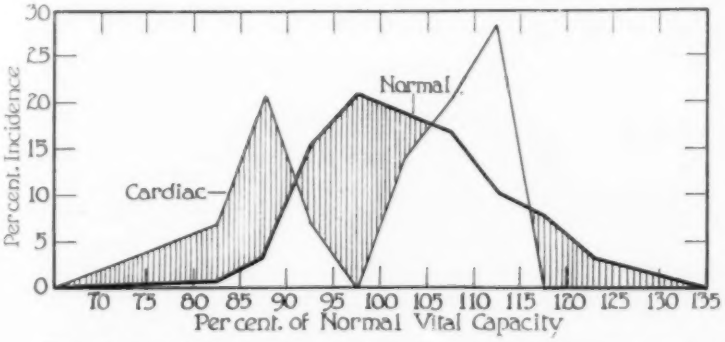

Chart 5.—Remaining effect of cardiac disease on vital capacity (fourteen cases).

4. Pneumonia varies but slightly in its effect on the vital capacity, according to the age contracted.

5. When pleurisy, pulmonary tuberculosis or organic heart disease is included among the past diseases of a group of persons, there is apparently a definite and probably a permanent lowering of the vital capacity of that group as a whole.

PROPERTIES OF YOUNG ERYTHROCYTES IN RELATION TO AGGLUTINATION AND THEIR BEHAVIOR IN HEMORRHAGE AND TRANSFUSION *

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In repeating the work of Ashby [1] while studying the length of life of red blood corpuscles by the transfusion and agglutination method, it was found that in many patients more than 1 per cent. of their red cells could not be agglutinated by serums, even before transfusion. The cells which did not agglutinate were found to consist of reticulocytes, normoblasts and cells with various types of "inclusion granules." The nature of these cells and their behavior under various conditions was studied in fifteen patients with various types of anemias in the wards of the Peter Bent Brigham Hospital, ten dogs and 130 normal persons.

The method of Ashby is based on the fact that the cells of Type II patients who have been transfused with Type IV (Moss) blood can be subsequently separated by agglutination with Type IV serum, which leaves the Type IV cells free. Under such conditions normal, nontransfused persons will have all of their cells agglutinated with the exception of about 20,000 to 50,000 per cubic millimeter, which remain free. Deducting this amount from the free cells of the transfused patient. Ashby, and more recently Wearn, Warren and Ames,[2] studied the blood of patients with various types of diseases, and found that, after transfusion, the minimum of 1 per cent. not agglutinated was not reached until from fifty-nine to 113 days, with an average of eighty-three days.

MATERIALS AND METHODS

The dog was found to be a suitable animal for experimental purposes. Ottenberg, Kaliski and Friedman [3] showed that dogs possessed iso-agglutinins and isohemolysins. Observations were also made on transfused and nontransfused human patients of different

* This paper is No. 31 of a series of papers on the physiology and pathology of the blood from the Harvard Medical School and Allied Hospitals, a part of the expense of which has been defrayed by a grant from the Proctor Fund for the Study of Chronic Disease.

1. Ashby, Winifred: The Determination of the Length of Life of Transfused Corpuscles in Man, J. Exper. Med. **29**:267 (March) 1919.

2. Wearn, Joseph T.; Warren, Sylvia, and Ames, Olivia: The Length of Life of Transfused Erythrocytes in Patients with Primary and Secondary Anaemia, Arch. Int. Med. **29**:527 (April) 1922.

3. Ottenberg, R.; Kaliski, D. J., and Friedman, S. S.: Experimental Agglutinative and Hemolytic Transfusions, J. M. Res. **23**:141 (May) 1913.

types, as well as on normal human beings. The blood of a group of ten dogs was matched, the corpuscles, serum and plasma of each being compared with serum, plasma and corpuscles of all the series. No effort was made to study type groups, although cases were found to correspond in their behavior to the four human groups, with an additional type in which two dogs would be mutually compatible (serum and corpuscles against corpuscles and serum) and thus apparently identical, but a third dog could be found whose serum agglutinated the corpuscles of one, but not the other. Dogs of this type, when transfused, were likely to have their type change suddenly after the transfusion, either to the type of the donor or to another type. Ottenberg, Kaliski and Friedman [3] noted similar changes of type in dogs. An effort was made to use dogs whose breed was fairly similar, although pure, pedigreed strains were not used.

The method of counting unagglutinated cells was originally that of Ashby, later modified to overcome some technical difficulties. The blood was taken from a razor cut at the base of the ear, at the same time of the day and before the dogs had any food or drink. United States Bureau of Standards pipets and slides were used to calibrate the apparatus used. Serum was stored in ampules made of glass tubing having a diameter of about 5 mm., and kept in a cold room (4 degrees) when not in use. The same serum was used throughout most of the parallel experiments, and new serums were checked up by comparison with the old. It was found that serum kept best when it was placed in larger ampules made of hard glass test tubes. When tubes are freshly drawn out in a flame, the inside becomes coated with a soluble base which makes the serum alkaline. It is necessary to wash this out and dry the tube. If alcohol or ether is used for drying, it must be thoroughly removed as traces dissolved in the serum hasten hemolysis when corpuscles are added.

In making the serum, blood was drawn into centrifuge tubes and centrifugalization at high speed was started before clotting took place. The corpuscles were separated, and on clotting a water-clear serum was obtained. Hemolysis takes place easily in dog's blood, and it was found necessary to separate the corpuscles quickly. Hemoglobin in the serum did not appear to influence the agglutination, but it was avoided in order to have the known factors as nearly similar as possible in different sets of serums.

Ashby's original method is, briefly, as follows: The blood of the recipient is drawn to the 0.5 mark in a leukocyte counting pipet, and is diluted to the 11 mark with 1 part of Group IV (Moss) serum in 20 parts of a 4.4 per cent. solution of sodium citrate. After thorough mixing, the contents are expelled into a small test tube and incubated for forty minutes at 37 C., with thorough shaking every ten minutes.

The test tube is then placed in the icebox over night. In the morning the mixture is shaken, and a drop transferred to the hemocytometer slide, and the free cells counted.

We found it necessary to modify this method for dogs as hemolysis set in after from three and one-half to four hours under the conditions of our experiments. It was also noted, in the case of human blood, that after shaking the test tube and pouring out the blood, many of the single, free corpuscles remained adherent to the test tube, as shown by examination of the tube under the microscope. The agglutination in dogs is much weaker than in human blood, and the clumps of cells are more easily disturbed by shaking.

The following method was then devised: Blood from the patient or animal was drawn up to the 0.5 mark in a leukocyte counting pipet, and diluted to the 11 mark with a 0.85 per cent. sodium chlorid solution in distilled water, containing also 0.2 per cent. sodium citrate. The first drop was blown out after thorough shaking, and the rest expelled into a small vial containing a glass bead. A red cell counting pipet having an accurately graduated stem was then selected, and the freshly shaken blood was drawn up to the 0.2 mark. Agglutinating serum was then drawn in until the solutions reached the 1 mark of the stem. This was then expelled on the table of a round moat type of hemocytometer slide, stirred with a glass rod (avoiding scratching of the ruled lines) and a grease-free cover applied. This was then kept in a moist chamber at from 18 to 22 C. and counts of nonagglutinated cells were made from time to time as in making an ordinary blood count. A duplicate set was always made. The serum was so chosen that it agglutinated the recipient's cells (when the patient or animal was transfused) but had no agglutinating effect on the donor's corpuscles.

The dilution of 2 parts diluted blood (1:20) to 8 parts of serum was chosen after many tests of varying dilutions, because this gives just enough cells to about cover the hemocytometer table (with a count of 5 million) without crowding. In the older method there was always a question of cells mechanically covered by clumps. In some experiments the cover was raised at intervals and the contents stirred. It was found, however, that the cells had enough motility to enter the clump formation without stirring. In control slides with a nonagglutinating serum and with the saline-citrate solution and serum there was no tendency to clump even after hours. The dilution error could be kept within 1 to 2 per cent. by this method.

Experiments were conducted to note the effect of varying hydrogen-ion concentrations. It was found that the buffering properties of the serum took care of all the probable variations of this technic. Serum made acid increased the rate of hemolysis, but agglutination was not more complete.

Temperature was found to vary the rate of hemolysis, so that if too warm, hemolysis set in before agglutination was complete. At the lower temperatures hemolysis was delayed, and the maximum agglutination was reached. Hemolysis and agglutination proceeded independently of each other. In dog's blood at temperatures above 22 C. it was found that hemolysis began before agglutination was complete under the conditions of these experiments.

Under these conditions, with the calcium bound by citrate in the diluted corpuscles, and with the traces of the animal's own plasma in the corpuscle suspension, the maximum agglutination with dog's blood was reached in from two and one-half to three and one-half hours at from 18 to 20 C. and in human beings in from twenty to twenty-four hours, a slight change taking place during the succeeding twenty-four hours.

The quantitative data concerning the rate of agglutination under the varying conditions are published separately.

Contact hemolysis (with glass) was avoided in this method by the protective action of the original and added serum, as demonstrated by Fenn.[4] Rouleau formation was a source of trouble with some serums. If a dog was transfused with a second dog's blood, and the serum of the second used to agglutinate the corpuscles of the first in subsequent examinations (as using a Type IV [Moss] serum to agglutinate Type II corpuscles in the man) the donors' corpuscles, meeting their own serum, formed rouleaux. Such cases could not be used for these data. However, the continued formation of rouleaux under these conditions gave a clue as to the survival of the donor's corpuscles, and they were not recognized after the third or fourth day by this method. Rouleau formation and agglutination may be seen simultaneously in preparations of blood from transfused patients or animals.

Experiments using serum from the same dog instead of saline solution for dilution showed little difference in the end-result, with the disadvantage of rouleau formation, which frequently took place in the serum. In dogs whose "type" changed after a transfusion, the serum or plasma, saved from blood taken before the transfusion, agglutinated the cells and thus could not be used for diluting purposes. This agglutination was not so complete as with a foreign serum.

To avoid the addition of any saline solutions or of sodium citrate, experiments were carried out using blood defibrinated with glass beads. This was soon found to be unsuitable, as there is a "selective" factor in which some of the cells (young forms) were not included in the

4. Fenn, Wallace O.: Hemolysis of Erythrocytes in Contact with Glass, J. Exper. Med. **35**:271 (Feb.) 1922.

strands of clot, whereas many mature forms were thus removed, producing a difference in the composition of the remaining cells.

Washed corpuscles were unsatisfactory in the dog, as hemolysis sets in quickly in dog's blood, and the relative composition (number of different types of red cells) was then changed.

Blood for transfusion in dogs was taken from the jugular vein and made to 0.2 per cent. sodium citrate, usually with the crystals, or in a few experiments with a 10 per cent. aqueous solution. Citration was used on the dog's blood, as this was the method used with the patients. Washed corpuscles were used in one experiment and the results compared with the whole blood. The blood was transfused through the jugular vein in the dogs, no anesthetic being used, as the dogs were very quiet and did not seem to be disturbed by the procedures. In making the daily counts, the dogs soon learned to jump on to the table and assume the proper position of their own accord.

It was soon found that after maximum agglutination of many patients' and some dogs' blood had been reached, there were often a great number of free, nonagglutinated cells, exceeding the 1 per cent. set as the normal by Ashby for human blood. All variations in technic were tried, and the percentage still remained high in nontransfused persons. The problem of the cells which would not agglutinate was then studied.

It was first noted that in bloods containing many reticulated red cells, the nonagglutinable cell number was greater than in bloods containing fewer of these cells. Quantitative studies were then started, comparing the number of cells which would not agglutinate with the number of reticulated cells. The latter were counted in smears vitally stained with cresyl blue and counterstained with Wright's stain using the details given by Cunningham.[5] Usually 1,000 cells were counted, occasionally more (10,000). A close correspondence was noted in the two figures, in spite of the many sources of error in these methods. With the reticulated cells, stippled cells, cells showing other basophilic phenomena and cells showing large intracellular, refractive granules were studied.

Intracellular granules of four types were differentiated in the red cells of human and dog's blood, in blood showing evidences of regeneration.

1. Brilliant, highly refractive large granules, In cresyl blue-Wright preparations they appeared black when the cell was in focus, and as a pink circle when the cell was out of focus. The granules may be confused with oil droplets and highly refractile débris, but these sub-

5. Cunningham, T. Donald: A Method for the Permanent Staining of Reticulated Cells, Arch. Int. Med. **26**:405 (Oct.) 1920.

stances, being on the surface, appeared refractile when the cell was in focus and black when the cell was not in focus. There was usually one to a cell, occasionally two. They were located either within the body of the cell or at its edge. They were frequently recognized free in the plasma in the fresh blood, or as a highly refractile granule within the corpuscles. When on the periphery the granule would adhere to any surface that it touched, giving rise to pear-shaped forms when the granule was single, and spindle-shaped forms when two granules were present, especially in fixed smears. The process could be followed in fresh preparations, sealed with petrolatum. The granules are much smaller than platelets, and are easily differentiated by their nonstaining qualities and high refractivity. With cresyl blue in the fresh, they have a pink reflex. The granules could be mashed from the cells and retained their identity in the serum. These granules are about the size of the granules of eosinophil leukocytes, sometimes slightly smaller. Cells containing these granules were among the last to hemolyze. They frequently showed diffuse basophilia. The granules were recognized in vitally stained normoblasts and in reticulated cells. In the normoblast they have a position by the nucleus suggesting a centrosome-like body or more nearly the centrosphere. Occasionally, in fresh preparations containing a few granules of brilliant cresyl blue, some of the bodies were recognized attached to the red cell by a thin pellicle, which, from its wrinkled character, showed it to be a membrane around the whole red cell, with the intact red cell inside, but separate from the refractive granule. This membrane stained heavily with eosin. The occurrence of these granules suggests young cells rather than degenerative cells. Smears of bone marrow from a young dog showed the refractive granules in 40 per cent. of the red cells. They were practically always present in normal blood (less than 1 per cent.). Pepper [6] described granules which apparently corresponded to these, in rabbits' blood, but noted them only after standing from twenty-four to forty-eight hours. In the fresh preparations the granules may be confused with the "knobs" of crenated cells. The "capsule-bodies" described by Schilling-Torgau [7] in the guinea-pig have some of the characteristics of these refractive granules, although in human and dog blood the structures are smaller than he has pictured the capsule bodies. He considers them related to the Ehrlich-Heinz bodies. In our fresh preparations it seemed evident that the refractive granules were inside the cell

6. Pepper, O. H. Perry: Observations on the Vitally Stainable Retriculation and Chromatic Granules in Erythrocytes Preserved in Vitro, Arch. Int. Med. **30**:801 (Dec.) 1922.

7. Schilling-Torgau, V.: Arbeiten über Erythrozyten. IV. Kapselköper, Pseudonukleoide, Innenkörper usw., sowie die Zentralkörnchen Gruppe in Säugetiererythrozyten, Folia Haematologica, Arch. Pt. 1 **14**:129 (Nov.) 1912.

proper in the "youngest" cells, and just underneath a limiting membrane at a later stage, and finally quite separated (attached only by a pellicle of this membrane) ultimately becoming dislodged and free. The granules measured about 1 micron in diameter (in fixed preparations). Unlike the Howell-Jolly bodies, they show just as clearly in films stained only with eosin.

2. Similar refractile granules, but much smaller, frequently two or more to a cell, commonly on the periphery, although also found on the interior.

3. Granules as large as the first kind, but nonrefractile and staining blue with cresyl blue-Wright combination; usually single and in the interior of the cell, occasionally two.

4. Granules similar to the foregoing, but much smaller, and frequently two or more.

Owing to the confusion in the naming of intracellular particles in the erythrocytes, it seems wisest to call the granules of Type I highly refractive, intracellular granules, in recognition of their outstanding characteristic. In some respects they can be identified with the Howell-Jolly [8] bodies, with Heinz [9] bodies, with the bodies described by Morris [10] as nuclear particles, by Schmauch [11] as "endoglobulare Körperchen" and by Schilling-Torgau [7] as "capsule bodies." These bodies, however, cannot be considered as taking any of the stains, as do the bodies described by these authors, although they appear colored because of the light reflex from their highly refractive substance, the tinge of color being determined by the surrounding color, sometimes similar, sometimes complementary. In this respect they never suggest nuclear particles, having no reaction in common with the nucleus. Their behavior in appearing during certain stages of anemia resembles the granules described by the various authors (Howell, Schmauch); their increase (at one stage) coincident with that of the basophilic granules in the red cells (Morris) is another point of similarity. They differ in being found in normal blood. Cells with refractile granules of Type I within their substance did not agglutinate. The question whether these cells mature in the circulation was studied in vitro, but the complicating factor of crenation made both agglutination and staining experiments in dogs difficult and of no conclusive value. In human blood there appeared to be a progressive increase in agglutination, reaching a

8. Howell, W. H.: The Life History of the Formed Elements of the Blood, Especially the Red Blood Corpuscles, J. Morphol. **4**:100 (July) 1890.

9. Heinz, R.: Morphologische Veränderungen der rothen Blutkörperchen durch Gifte, Virchows Arch. f. path. Anat. **122**:112 (Oct.) 1890.

10. Morris, Roger S.: Nuclear Particles in the Erythrocytes, Arch. Int. Med. **3**:93 (March) 1909.

11. Schmauch, G.: Ueber endoglobuläre Körperchen in den Erythrocyten der Katze, Virchows Arch. f. path. Anat. **156**:201 (May) 1899.

maximum when the number which was that of the refractive granule cells was reached, after two or three days. This, at least, is suggestive that the cells with reticulum inside may change their properties with age, although, of course, these conditions are quite abnormal.

Dogs that were given transfusions with corpuscles which could be separated by an agglutinating serum and patients who were transfused were followed, comparing the nonagglutinated cell count with the count of cells showing reticulation, nucleation and refractile bodies within the

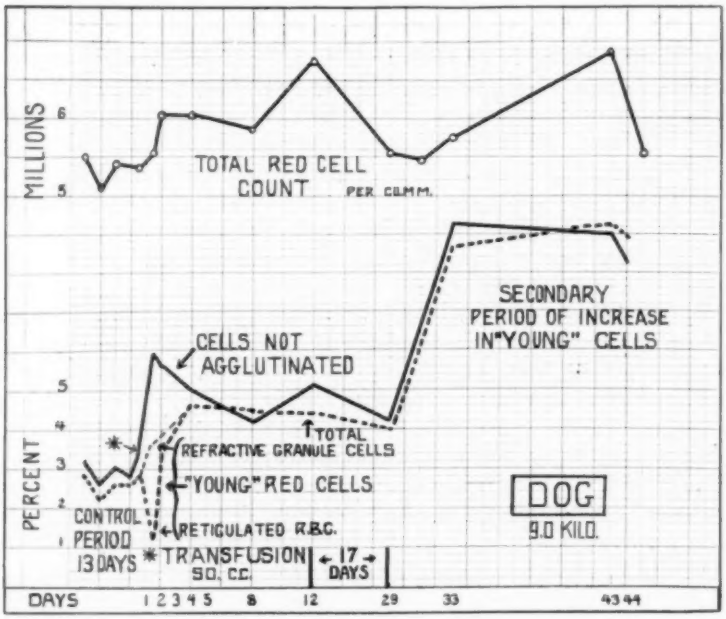

Fig. 1.—Showing rise in number of refractive granule red cells and temporary fall in number of reticulated red cells in comparison with the total nonagglutinable cells in a dog receiving 50 c.c. of compatible blood of a different agglutination type, without previous bleeding. A secondary rise in young and in nonagglutinable cells after thirty-three days.

cell. It was found that immediately after the transfusion (Figs. 1, 4 and 5) the total count of cells showing the reticulum fell, but the number of young cells equaled the number of nonagglutinated cells within from two to four days, and ran parallel after this, so that further counts of nonagglutinated cells could no longer be considered as representing the donor's cells. The donor's blood in most cases contained less than 1 per cent. of reticulated cells. Dogs were then bled so that there was

a rise in the number of young cells; a parallel rise in both non-agglutinated and young cells was noted (Fig. 2).

Preparations were then made of nontransfused corpuscles and an agglutinating serum, and two series were made—one for making counts of the progress of agglutination and the other for staining to determine the character of the nonagglutinated cells. Figure 3 shows that, while after twenty minutes only 3 per cent. of the nonagglutinated cells showed diffuse basophilia, stippling, nuclei, reticulum and refractile

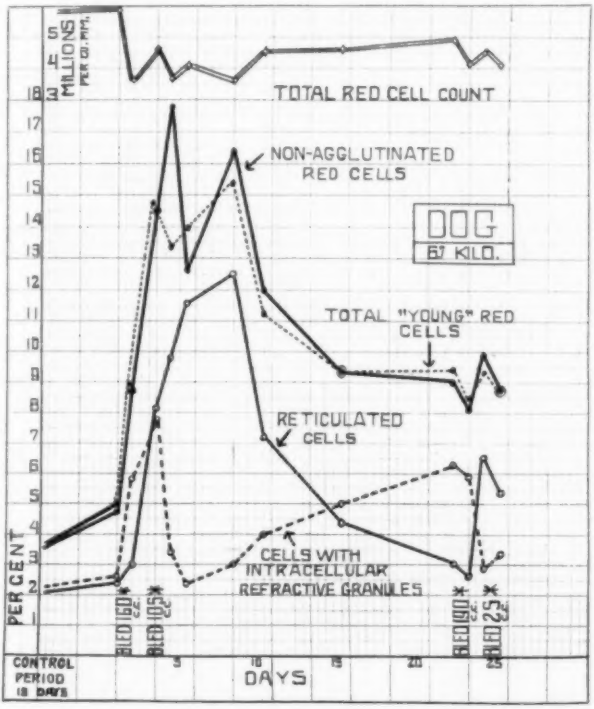

Fig. 2.—One of a series of dogs subjected to hemorrhage. A temporary rise in the refractive granule red cells, until the supply is exhausted, is noted after the first hemorrhage, and inverse relation between the refractive granule red cells and reticulated red cells in hemorrhage and recovery is shown. The nucleated red cells remained below 1 per cent. The numerical relation between the "young" cells and the nonagglutinated cells is shown.

bodies within the cell, the proportion rose rapidly until finally 70 per cent. of the nonagglutinated cells were of this kind. After this period the reticulum stained as coarse granules in wet preparations. In other words, as the other cells were gradually drawn into the clumps, the cells with basophilic phenomena and refractile bodies remained free.

The forms found corresponded to those of fresh preparations, and did not appear to be degenerative effects. In making this test, it is essential to be sure that there is no rouleaux formation, as the reticulated cells are excluded from the rouleaux and give an almost similar picture.

Two human cases were apparent exceptions, in that, although the reticulated count was high, the agglutination was complete. It was found that both patients had a large percentage of macrocytes and megaloblasts, and vital staining with cresyl blue showed that reticulated

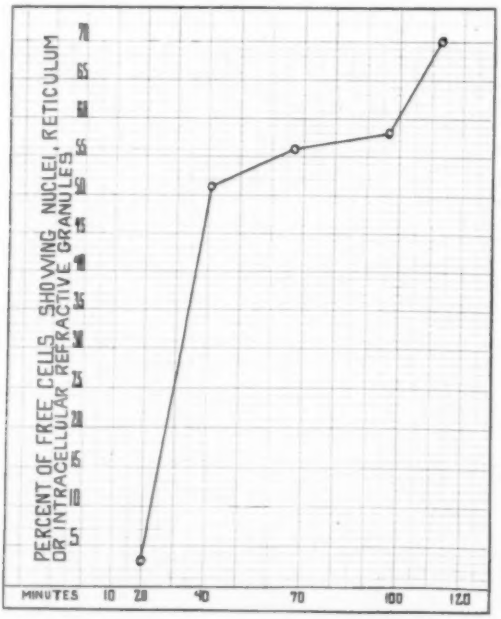

Fig. 3.—One of a series of analyses of the nonagglutinated cells with supravital staining with brilliant cresyl blue. Twenty minutes after mixing the corpuscles of this dog with an agglutinating serum, 3 per cent. of the red cells which were not yet agglutinated showed internal bodies of some kind. After two hours, 70 per cent. of the few cells which still remained free showed these structures.

macrocytes differ from reticulated normocytes in being included in the agglutinated clumps. Cells in which the refractile bodies were at the periphery were sticky and adhered to the groups.

In normal blood from human beings and dogs, the number of non-agglutinable cells after twenty-four hours was around 1 per cent. and ran fairly parallel to the number of cells showing reticulation and refractile bodies within the cell.

The immediate effect of a transfusion of from 65 to 135 c.c. of blood in an 11 kilogram dog from a dog of the same type and the same breed was an immediate increase in the refractile granule cells and a decrease in the reticulated cells for one or two days, followed by a rise. This was true whether the dogs were bled previously and transfused with the same amount or were given the transfusion without previous bleeding (Fig. 4). The drop in reticulocyte number was similar to that found by Vogel and McCurdy,[12] Robertson [13] and by Krumbhaar

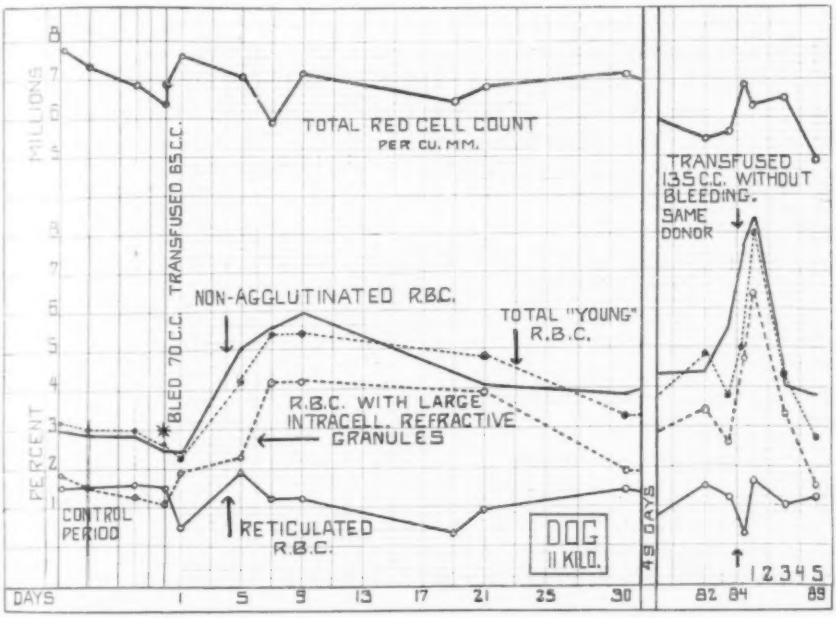

Fig. 4.—One of a series of dogs given transfusions with and without previous bleeding. This dog was transfused with blood of the same agglutination type. The relation of the reticulated red cells, the refractive granule red cells, the total young cells, the nonagglutinable cells and the total red count is shown.

and Chanutin [14] in experimental plethora, but it occurred in animals which had been previously bled and theoretically were not plethoric. The sudden anemias developing in animals that have been previously

12. Vogel, Karl M., and McCurdy, U. F.: Blood Transfusion and Regeneration in Pernicious Anaemia, Arch. Int. Med. **12**:707 (Dec.) 1913.

13. Robertson, Oswald H.: The Effects of Experimental Plethora on Blood Production, J. Exper. Med. **26**:221 (Aug.) 1917.

14. Krumbhaar, E. B., and Chanutin, Alfred: Studies on Experimental Plethora in Dogs and Rabbits, J. Exper. Med. **35**:847 (June) 1922.

repeatedly transfused (Robertson) was noted in one of our dogs between the twenty-ninth and thirty-second day after a single transfusion (Fig.1). In this case, 50 c.c. of blood were given to a dog weighing 9 kilograms, without previously bleeding. The rise in reticulated count, and incidentally in the nonagglutinated cells, is shown in Figure 1. The first part of this curve shows the response of the "young" red cells when the bloods are compatible, but of different types, as when a Type II patient is transfused with a Type IV (Moss) blood.

The relation between the number of red cells not agglutinated, the number of cells showing only refractile granules and those cells showing a reticulum (many of which contained refractive granules) after hemorrhage is shown in Figure 2. This was a dog which was subjected to several hemorrhages, without replacement of fluid with salt solution, the number of red cells showing only refractive granules first increased, then decreased, while the reticulocytes increased; but with improvement in the condition, the reticulocytes decreased with increase in the cells showing only refractive granules inside of the cell. In our series of dogs, the increase in normoblasts was slight during any of the experiments, being less than 1 per cent.

Figure 5 shows the response of the immature cells in a case of secondary anemia (mitral stenosis, uterine fibroids). The patient, Type II, received 400 c.c. of Type IV (Moss) blood. Just after the transfusion, the refractive granule red cells in the circulation increased in number, and began to decrease after the second day, when the reticulated cells began to increase in number. The sum of the two types about equaled the number of the nonagglutinable cells on the fourth day, and ran fairly parallel after that. Figure 5 also shows a case of pernicious anemia in which, after a transfusion of 650 c.c., there was a fall in the number of reticulated cells in the peripheral circulation, accompanied by a temporary rise in the number of refractive granule red cells. Here, also, the total number of immature cells equaled the number of nonagglutinable cells after the fourth day, and the numbers ran parallel after that. The difference between the total number of young cells and total number of nonagglutinable cells during the first four days probably represents the foreign cells in the circulation. The types of the nonagglutinated cells, in these and in the other preparations, was determined by supravital staining with cresyl blue, and the examination of the wet preparation sealed with petrolatum.

In the case of pernicious anemia shown in Figure 5, the number of reticulated cells did not show much evidence of activity, although the fact that the total red cell count did not decrease shows that cells were being supplied to the circulation. Evidently during the first eleven days, in this case, the cells matured in the blood-forming organs before

they were discharged into the circulation. Later the more immature cells started to come to the peripheral blood.

In these preparations, the counts of the nonagglutinated cells were the maximum number not agglutinated. This was determined by making repeated counts during the course of three or more hours, and the maximum determined by direct observation.

The relative numbers of the different types of cells in the peripheral circulation was considered as not being dependent on the total blood

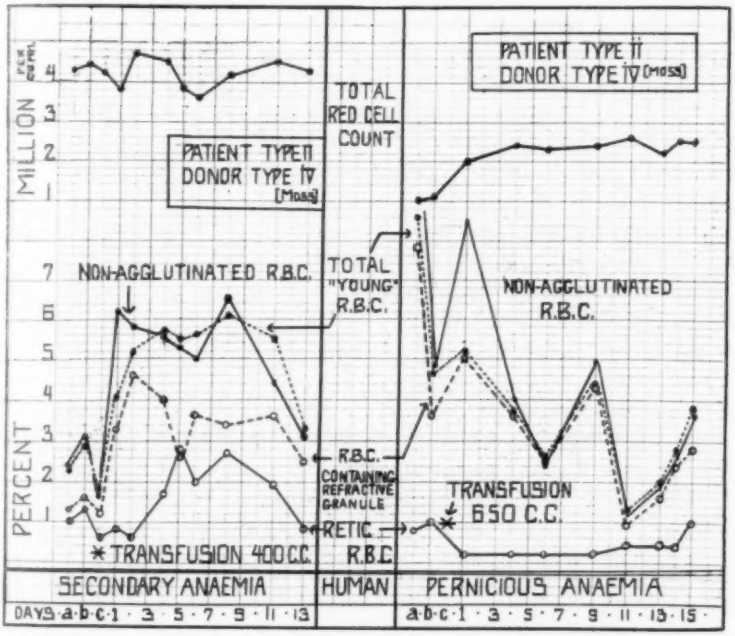

Fig. 5.—Two of a series of patients with anemia. The curves represent individual cases, and the differences have probably no intrinsic significance in the differential diagnosis of the cause of the anemia.

volume, and the latter was not determined in these experiments. The difference in composition of the blood in different parts of the body was not taken into account, as the data are comparative and represent capillary blood taken from the same region for each observation.

COMMENT

The fact that certain red cells—the forms classed as young cells—may not agglutinate with agglutinating serums accounts for the high

counts obtained in some nontransfused persons. It also means that the counts of cells (after the number of cells showing basophilic phenomena and refractive bodies within the cell has reached the number of nonagglutinable cells in a transfused patient) are of little value from the point of view of following the donor's cells. After from two to four days no definite statement can be made as to the persistence of the donor's cells. The counts plotted out in these cases merely show the response of the patient in being able to produce young cells. These cells frequently decreased as the patient's blood count increased in from several weeks to three months in the cases reported. Thus in Case B reported by Wearn, Warren and Ames,[2] when the blood count reached 4,556,000 (111 days after a transfusion) the percentage of nonagglutinable cells fell to 0.77 per cent.

These observations also offer an explanation of the irregular curves obtained by Ashby,[15] and by Wearn, Warren and Ames [2] with rises and falls in the number of supposed donor's cells, and explain the fact that after a Type II patient was transfused with Type II blood (Case A, Wearn, Warren and Ames) the nonagglutinable cells rose almost as high as when Type IV (Moss) cells were given, using Type IV serum in both cases to agglutinate the cells (Fig. 4, dog experiment).

Ashby recognized the variation in the response to agglutination in nontransfused persons, noting that the counts of "corpuscles lying between clumps is usually from 0.5 to 0.7 per cent. of the total blood count, but it may vary in different bloods from 0.03 to 3.4 per cent."

It is interesting to note the difference in the behavior of the reticulated macrocytes and megaloblasts and normocytes and normoblasts. Another differential characteristic was pointed out by Morris and Thayer [16] in the ability of the macrocytes to change their shapes.

The property of nonagglutination is, then, possessed in common by reticulated normocytes, normoblasts, stippled cells, cells with refractive bodies within the cell substance, and is a property of immature red cells. The formation of pointed cells in smears from these cells indicates that all poikilocytosis does not indicate blood destruction, as these cells are among the last to hemolyze.

Key [17] described reticulated cells of the rabbit as having a tendency to agglutinate with each other and to adhere to foreign bodies in the blood, particularly in oxalated blood in hypotonic salt solution. He

15. Ashby, Winifred: The Periodicity in Eliminative Activity Shown by the Organism, J. Exper. Med. **34**:127 (Aug.) 1921.

16. Morris, Roger S., and Thayer, William S.: Amoeboid Movements in Macrocytes and Megaloblasts, Arch. Int. Med. **8**:581 (Nov.) 1911.

17. Key, J. Albert: Studies on Erythrocytes with Special Reference to Reticulum, Polychromatophilia and Mitochondria, Arch. Int. Med. **28**:511 (Nov.) 1921.

noted that the reticulated cells had a tendency to rise, being lighter than normal erythrocytes. Toward agglutinating serum, however, the behavior appears to be different. Whether the specific gravity factor plays much of a part in this separation is questionable.

The fact that there was little difference in the response of dogs which had been bled immediately before transfusion and those which were transfused without previous bleeding and in dogs in which the same or a different (but compatible) type of corpuscles were used suggests that the transfused cells last only a short time—a few days at the maximum, and that their rapid disappearance leaves the animal in a potentially anemic condition, "calling out" the production of young cells. The "rest" which the marrow has had for a day, together with the improved conditions which the donor's corpuscles bring about while they are present, enables the marrow to respond to a stimulus which, in anemic cases at least, was inadequate before. The production of many young cells in animals having presumably the normal number of red cells suggests this view.

Boycott and Douglas [18] and also C. Drinker, K. Drinker and Kreutzmann [19] have pointed out that following a hemorrhage in dogs there is a tendency to over-regeneration, with the eventual production of polycythemia. As our studies show that after transfusion the picture becomes much like that after hemorrhage, the "stimulating" effect of transfusions must probably lie in this factor.

In response to a "call" for young cells, either after transfusion or after hemorrhage, the first cells to be delivered are those containing the large refractive granules; then the reticulated cells appear in increased amount. As these contain refractive granules in many cases, the drop in the number of refractive granule cells (Fig. 2) is only apparent. Finally, the nucleated red cells increase. During recovery, the disappearance or reduction is in inverse order. The cells containing only the refractive granules are then the final stage in the maturation of a red cell, and their number in the circulation is a fair indication of the rate of blood production during health (data published elsewhere), and their relative number is of prognostic importance in conditions of blood regeneration. An increase in their number, with a decrease in the number of reticulocytes and normoblasts, indicates that conditions are

18. Boycott, A. E., and Douglas, C. G.: On the Carbon Monoxide Method of Determining the Total Oxygen Capacity and Volume of Blood in Animals, with Some Experiments on Anaemia and Transfusion, J. Path. & Bacteriol. **13**: 275, 1909.

19. Drinker, Cecil K.; Drinker, Katherine R., and Kreutzmann, Henry A.: The Factors Concerned in the Appearance of Nucleated Red Blood Corpuscles in the Peripheral Blood. II. Influence of Procedures Designed to Increase the Rate of Blood Flow Through the Blood-Forming Organs—Hemorrhage and Infusion, J. Exper. Med. **27**:395 (March) 1918.

returning to normal, whereas their decrease suggests that cells are being used before maturity or that an aplastic condition is developing, if accompanied by a decrease in the more immature forms.

The resistance to agglutination is probably not due to absence of so-called agglutinogens but to a demonstrable membrane around the immature cell.

These findings are of practical interest in giving an additional laboratory prognostic sign in hemorrhage and anemia and of indicating a possible source of error in assuming that bloods are compatible, whereas in reality the increase in young forms may be the cause of readings of weak agglutination or no agglutination when the compatibility tests are made under other than ideal conditions. It is possible that some reactions, especially in subsequent transfusions, may have their origin in improper readings from this cause.

SUMMARY AND CONCLUSION

For blood of man and dog:

1. Reticulated normocytes are not agglutinated by serums that affect the other red corpuscles.

2. Normoblasts and cells containing large highly refractive granules within the cell are not agglutinated.

3. The use of agglutination in recognizing the cells of a donor in a mixture of two bloods in a transfused patient is of little value after the number of young cells reaches the number of nonagglutinable cells, usually in from two to four days.

4. Reticulated macrocytes and megaloblasts do not follow the behavior of the reticulated normocytes toward agglutinating serums.

5. Nonagglutination is a property which is evidently common to immature red cells.

6. Cells showing highly refractile intracellular granules are young cells. Owing to the adhesive nature of the granules when they are peripheral, the cells frequently show pear-shaped or spindle-shaped forms in stained smears.

7. Cells showing only the refractive granules represent the final stage in the production of mature red cells, and their increase, with a decrease in reticulocytes after hemorrhage or hemolysis, indicates a return to normal, whereas their decrease, with an increase in the reticulocytes, is indicative of the continuation of the effects of the disease process.

8. The resistance to agglutination is probably due to a demonstrable membrane around the immature cell.

9. After hemorrhage, the cells showing the large intracellular refractive granules are the first to be delivered into the circulation, then the reticulated cells (many of which contain the granule), and

finally the nucleated red cells. Disappearance during recovery is in the reverse order.

10. After a transfusion, the process is similar, the effect being that of a potential hemorrhage.

11. The reduction of the number of reticulated cells immediately after a transfusion, with an increase in the number of cells showing the refractive intracellular granule, suggests that one of the temporary effects of a transfusion is to allow the forming red cells time to advance one step further in their process of developing into a mature cell. The transfusion then does not depress the erythropoietic tissue, but temporarily makes it more normal.

ALIMENTARY LEUKOCYTOSIS IN VARIOUS PATHOLOGIC CONDITIONS

A FURTHER STUDY IN REFERENCE TO THE CRISE HÉMOCLASIQUE OF WIDAL *

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BROOKLYN

This report is based on the use of the Widal test for hepatic insufficiency in a group of fifty patients with miscellaneous conditions. It represents the second phase of a study suggested to me by the statement by Widal, Abrami and Iancovesco [1] in 1920 that leukopenia following a standard protein meal is to be regarded as a delicate test for insufficiency of the liver.

The technic of the test proposed by Widal is simple. The subject to be examined abstains completely from food for a period of at least five hours preceding the test. This detail is of great importance, as the ingestion of nitrogenous food, no matter how small the amount, interferes greatly with the reaction. A leukocyte count is made, and then the subject drinks 200 gm. of milk (a glass of milk, the exact amount not being essential). Subsequently, the leukocytes are counted at intervals of twenty minutes (the author uses half hour intervals) for a period of two hours. Normally, there is a slight leukocytosis following the ingestion of the milk, and the count never falls below the prealimentary level. The occurrence of postalimentary leukopenia is considered pathologic and an evidence of hepatic insufficiency. This leukopenia when present, usually appears in the first hour.

The principal experimental data on which Widal's test is based include the production of a crise hémoclasique (1) by the injection of commercial peptone into the general circulation of a dog; (2) by the establishment of an anastomosis between the portal vein and the inferior vena cava of a dog during the digestive period, under which conditions no crisis occurs in unfed controls, and (3) by the introduction of blood from the portal vein of a dog during the height of the digestive period into the saphenous vein of the same animal. The syndrome of the crise hémoclasique, which is attributed to an upset of the colloidal balance of the blood, is characterized by leukopenia, a fall of blood pressure, hypercoagulability, and a change in the refractive index of the serum. The

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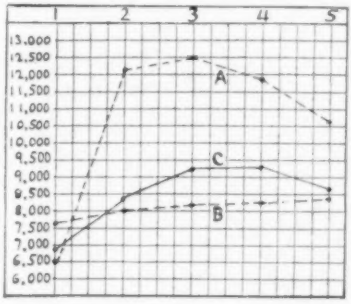
1. Widal, F.; Abrami, P., and Iancovesco, N.: L'Épreuve de l'hémoclasie digestive dans l'étude de l'insuffisance hépatique, Presse méd. **28**:893 (Dec. 11) 1920.

most important component of the reaction, and the one on which the clinical test is built, is the fall in the leukocyte count.

On the basis of his investigations, Widal formulated the hypothesis that one of the functions of the liver, the proteopexic function, is to arrest the peptones, proteoses and other disintegrating protein substances found in the portal vein during the digestive period and to transform them into an innocuous form. A deficiency of the proteopexic function allows the entrance of split protein products into the general circulation, causing the disturbance of colloidal balance which is manifested clinically by the phenomena of the hemoclasic crisis.

In a previous communication, the author [2] reported a study of postalimentary leukocyte curves in eighty normal persons. In every instance, some degree of leukocytosis followed the consumption of the glass of milk; in other words, the crise hémoclasique, as judged by the



Postalimentary leukocyte curves in eighty normal persons: 1, after five hours' fast and before test meal; 2, one-half hour after milk; 3, one hour after milk; 4, one and one-half hours after milk; 5, two hours after milk; *A*, maximal degree of leukocytosis; *B*, minimal degree; *C*, composite curve of leukocytosis in eighty normal persons. In every instance, some degree of leukocytosis was observed. The interrupted lines *A* and *B* represent the limits of variation; that is, they are the curves of the cases in which the maximal and the minimal degrees of leukocytosis, respectively, occurred. The solid line *C* represents the composite curve of normal postalimentary leukocytosis, the average of the curves obtained.

postalimentary leukocyte curve, did not once occur in a normal person. There was considerable uniformity in the curves. The chart shows the composite curve given by these eighty normal subjects, together with the two extreme variants.

The literature appertaining to digestive hemoclasis is voluminous and, to a large extent, contradictory, and it would be an unprofitable

2. Feinblatt, H. M.: Alimentary Leukocytosis in Eighty Normal Men. A Study in Reference to the Crise Hémoclasique of Widal, J. A. M. A. **80**:613 (March 3) 1923.

task to review it. In general, French authors find the test of value in the differentiation of conditions affecting the intestinal tube and its appendages, and they appear to have established the fact that the crise hémoclasique disappears with the removal of its cause. For example, digestive hemoclasis is consistently associated with cholelithiasis, but disappears a month or so after removal of the gallbladder. Other workers, particularly in Germany, fail to obtain consistent results with this test.

TABLE 1.—*Cases Yielding a Typical Crise Hémoclasique*

No.	Sex	Age	Clinical Diagnosis	Before Milk	After 200 Gm. of Milk ½ Hour	1 Hour	1½ Hours
1	F	28	Bronchial asthma	8,600	8,400	8,000	7,200
2	M	50	Laennec's cirrhosis	4,000	2,800	2,800	1,600
3	M	38	Cholelithiasis	10,000	7,600	5,200	6,000
4	M	35	Syphilis of liver; ascites	8,000	7,200	7,200	6,500
5	M	24	Idiosynerasy to milk; sick with nausea, apparently due to test meal	12,400	10,400	8,450	.....
6	M	42	Laennec's cirrhosis; bronchitis	20,000	15,400	11,200	.....
7	M	25	Bronchial asthma; positive skin reactions to many food proteins	12,600	12,400	10,000	11,000
8	F	25	Hay fever; sensitive to ragweed, goldenrod and rye	11,200	10,600	8,200	8,600
9	M	30	Chronic otitis media; took ½ grain calomel on day preceding test	10,000	7,000	6,200	10,000
10	F	48	Passive congestion of liver; auricular fibrillation	10,400	6,800	7,200	13,000
11	F	33	Mitral stenosis	7,400	5,600	7,000	7,800
12	M	23	Arthritis of ankle	11,800	9,200	11,000	12,400
13	M	62	Chronic alcoholism	8,000	7,000	6,400	6,600
14	M	53	Bronchial asthma	9,200	5,800	11,800	13,000
15	M	64	Sciatica; pleurisy	8,200	5,800	6,400	7,400
16	M	62	Pneumonia; jaundice	24,000	24,000	19,800	23,600
17	M	62	Pneumonia; jaundice	37,400	27,600	24,200	41,400
18	F	42	Arthritis deformans	10,600	8,000	9,000	11,000
19	M	13	Essential epilepsy	6,000	6,000	5,800	5 900
20	M	46	Arthritis deformans	7,000	6,600	6,600	6,400
21	M	44	Neurocirculatory asthenia	5,000	4,400	3,800	5,400
22	F	42	Bronchial asthma; all skin tests negative.	11,000	11,000	8,400	8,800

SCOPE OF THIS STUDY

The object of this investigation was not specifically to study the Widal test with reference to insufficiencies of the liver, but to examine a miscellaneous group of patients in the hope that leads for further study might thus be furnished. The fact that in a consecutive series of eighty normal persons a crise hémoclasique did not once occur establishes the fact that this phenomenon must necessarily be construed as pathologic; but, depending, as it does, on an upset of the colloidal balance of the blood, the crisis might conceivably result from a great variety of abnormal states.

The Widal test was performed on fifty patients suffering from various conditions. According to the type of postalimentary leukocyte curve attained, the patients were classified into three groups as follows: (1) those yielding a frank crise hémoclasique (relative leukopenia one-

half and one hour after the test meal); (2) those yielding a normal curve (relative leukocytosis one-half and one hour after the test meal); and (3) those yielding an indeterminate curve.

The data presented in the foregoing tables are sufficient to show that the hemoclasic crisis may occur in a great variety of conditions in which hepatic insufficiency is not evident on clinical examination. These

TABLE 2.—*Cases Yielding a Normal Response in Postalimentary Leukocytosis*

No.	Sex	Age	Clinical Diagnosis	Before Milk	After 200 Gm. of Milk		
					½ Hour	1 Hour	1½ Hours
1	M	23	Essential epilepsy	11,800	12,000	13,000	15,200
2	M	13	Essential epilepsy	10,800	11,400	14,000	14,200
3	F	24	Mitral stenosis with decompensation; pregnancy	7,400	11,400	9,200	8,600
4	F	48	Arthritis deformans; pulmonary tuberculosis; old carcinoma of breast	7,400	7,800	8,000	8,400
5	F	49	Carcinoma of bronchus	6,600	8,000	10,000	9,400
6	F	50	Hyperthyroidism; myocarditis	7,400	7,600	10,000	8,000
7	F	22	Toxic polyneuritis	6,600	9,000	9,400	7,800
8	F	39	Chlorosis	7,400	8,000	8,200	9,000
9	M	21	Malaria	4,800	6,200	7,600	7,000
10	M	55	Gastric ulcer	7,200	7,200	8,200	7,400
11	M	55	Chronic glomerular nephritis	7,200	8,600	9,200	6,400
12	M	21	Diabetes mellitus	9,600	11,200	9,200	13,200
13	M	39	Syphilitic arthritis	9,800	10,400	11,000	9,000
14	M	32	Arthritis	8,000	9,000	8,200	9 000
15	M	45	Raynaud's disease	8,000	8,000	10,400	9,800
16	F	32	Trichinosis	12,000	17,600	11,800	11,600

TABLE 3.—*Cases Yielding an Indeterminate Curve*

No.	Sex	Age	Clinical Diagnosis	Before Milk	After 200 Gm. of Milk		
					½ Hour	1 Hour	1½ Hours
1	M	27	Bronchial asthma	9,000	10,000	6,400	7,000
2	M	60	Aortic insufficiency	12,700	11,800	15,000	15,000
3	M	40	Hodgkin's disease	8,100	9,400	7,200	10,200
4	M	68	Uremia; chronic myocarditis	8,200	9,600	7,400	8,400
5	M	55	Passive congestion of liver; cardiac decompensation	8,600	8,800	8,400	9,600
6	M	43	Cardiac decompensation; hydrothorax and enormously enlarged liver	10,400	10,800	8,000	9,000
7	M	60	Pernicious anemia	3,000	3,200	2,500	2,950
8	F	38	Brain tumor	9,400	9,000	9,000	9,000
9	F	45	Diabetes mellitus; hypothyroidism	8,200	8,400	8,000	8,000
10	F	37	Hypothyroidism	8,400	8,200	8,800	7,600
11	M	53	Urticaria	6,600	6,000	10,800	8,000
12	M	47	Perihepatitis	9,720	10,340	8,200	8,000

results, of course, have no great bearing on the validity of the Widal test. In the first place, a considerable degree of anatomic damage to the liver can escape detection by clinical methods, and in the second place, the crisis is supposed to be due to a functional defect of the liver, which would be not in the least incompatible with an organ showing no lesions at necropsy. This test is based entirely on biologic principles. The hemoclasic crisis is evidently a nonspecific anaphylactic reaction, which experimental evidence has shown can be produced by the entrance of portal blood into the general circulation and can be prevented by the

action of the liver on such blood. It is unfair to apply anatomic standards to such a test, except so far as it must be acknowledged that deficiency of function is much more apt to be present in an organ badly damaged.

Many workers, particularly in Germany, having obtained results similar to mine, that is, a hemoclasic crisis in conditions not related to the liver, have been inclined to discredit the whole test. To me this attitude does not appear justified. It undoubtedly is fair to conclude from the evidence that a positive crisis does not necessarily mean that the liver is badly damaged, especially in view of the fact that in certain diseases of the digestive tube and its appendages, for example in cholelithiasis, the hemoclasic reaction disappears with the removal of the cause. Furthermore, the crisis can in no sense be construed as indi-

TABLE 4.—*Summary of Clinical Diagnosis in Twenty-Two Patients Showing the Crise Hémoclasique*

Bronchial asthma	4
Laennec's cirrhosis	2
Arthritis deformans	2
Pneumonia with jaundice	2
Cholelithiasis	1
Syphilis of liver with ascites	1
Idiosynerasy to milk	1
Hay fever	1
Otitis media (calomel ?)	1
Passive congestion of liver, auricular fibrillation	1
Mitral stenosis	1
Arthritis of ankle	1
Alcoholism	1
Sciatica and pleurisy	1
Essential epilepsy	1
Neurocirculatory asthenia	1
Total	22

cative of a general reduction of hepatic function, but rather of a deficiency of one particular function, the proteopexic function. It is for this reason that it would be a fruitless task to make a parallel study between the Widal test and other tests of liver function, such as the phenoltetrachlorphthalein method.

In two cases in which the patients, both of whom appeared clinically to be suffering from advanced hepatic disease, came to necropsy, the Widal test was of value in the differential diagnosis.

REPORT OF CASES

CASE 1.—J. A., a man, aged 59, married, whose history, physical signs and laboratory findings established the diagnosis of taboparesis, further exhibited considerable enlargement of the abdomen together with the signs of ascites. Paracentesis yielded a thick, mucilaginous fluid, which contained 0.2 gm. of albumin per liter, was sterile, and showed a few polymorphonuclear and many undifferentiated cells. The Widal test gave a curve of 10,000 cells before the ingestion of milk, and 10,000, 12,000 and 13,000 cells, respectively, at one-half hour intervals afterwards, that is a normal response. At necropsy the cause

of the ascites was found to be a myxoma involving the omentum and the intestines. Except for slight congestion and amyloid change, the liver was normal.

CASE 2.—T. J., a man, aged 53, married, who gave a history of a syphilitic infection eighteen years prior to admission, had suffered for a period of one year from occasional vomiting, followed in the course of several months by weakness, a tremor of the hands, loss of appetite, and, a few days before admission, by jaundice. He had always been a heavy drinker. On physical examination, the liver could be palpated four fingerbreadths below the costal margin; there was a definite yellowish tinge to the sclerae. The Widal test gave a curve of 22,400 cells before the ingestion of milk, and 15,800 and 11,800 cells respectively at one-half hour intervals afterward, that is, a frank hemoclasic crisis. The patient died of a hypostatic pneumonia. Necropsy revealed evidence of advanced hepatic damage. Sections from the liver, which was markedly enlarged, showed considerable perilobular and intralobular fibrosis, with marked regeneration and reduplication of the smaller bile ducts. The lobules were irregular in contour, and the majority of them showed fatty infiltration.

THE VARIABILITY OF THE LEUKOCYTE CURVE

One point which becomes apparent from an examination of the tabulation seems to be of great practical importance, namely, the variability of the leukocyte curve. It appears that the relation of the white blood cell count to the digestive phases will have to receive greater emphasis. So marked are the fluctuations which may follow nothing more than the ingestion of a glass of milk that our clinical deductions may often prove to be erroneous unless we make proper allowances. Thus one patient, a man, aged 62, with lobar pneumonia, yielded a count of 37,400 cells before ingestion of milk and of 27,600, 24,200 and 41,400 cells, respectively, at one-half intervals afterward. Certainly a variation of 17,200 cells in the short space of one-half hour might lead to a different interpretation one way or the other in cases in which only a single specimen is taken. It may, perhaps, prove eventually to be more reliable to make our inferences from a leukocyte curve rather than from a single count.

CONCLUSIONS

1. The crise hémoclasique of Widal, as evidenced by the postalimentary leukocyte curve, does not occur in normal subjects.

2. The hemoclasic crisis has been observed by many workers in patients who showed no clinical evidence of hepatic disease. My results have been in accord with this general trend. It appears established that this test can in no way be used to measure quantitatively gross organic damage to the liver.

3. The Widal test should be considered as relating not to liver function in general, but to one particular liver function, the proteopexic function.

4. The proteopexic function is deficient when there is gross organic damage to the liver; frequently it is deficient when there is no other evidence on which to indict the liver.

5. The interpretation which should be placed on a positive crise hémoclasique is that it indicates a functional defect of the liver, perhaps transitory, which gives rise to a nonspecific anaphylactic reaction.

6. Protein ingestion may give rise to marked oscillations in the leukocyte count. In one patient with pneumonia, there was a variation of 17,200 cells in half an hour. In interpreting the white blood cell count, the influence of the phases of digestion must be accorded proper consideration.

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BLOOD AND PLASMA VOLUME IN OBESITY

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Few estimations of blood volume have been made on obese persons, but those obtained have indicated a small blood volume in comparison with body weight. Haldane and Smith [1] were the first to draw attention to this fact. Later, Keith, Rowntree and Geraghty [2] showed that both the blood and plasma volumes were small in certain obese patients. Rasmussen and Rasmussen [3] compared the blood volume in the woodchuck in midsummer, just before and during hibernation, and found that there was a relative reduction in blood volume when a maximum amount of fat was stored within the body. Our observations on a series of obese patients have confirmed this relationship between blood volume and excessive deposits of fatty tissue. In the present series, patients were also studied after they had lost a known amount of weight, chiefly to determine whether loss of weight brought about constant changes in blood and plasma volumes. Fourteen cases were followed over a period of several weeks, volumetric studies being made before reduction and following a loss of from 5 to 15 kg. in weight. The results revealed interesting facts concerning the relationship between blood and plasma volume and obesity, and are reported here.

TECHNIC EMPLOYED

The total circulating volume of blood and plasma was determined by the dye method of Keith, Rowntree and Geraghty. Vital red and Congo red were both used and gave equally satisfactory results. Harris [4] found that Congo red leaves the blood vessels of cats and dogs less rapidly than does vital red. This has not been our experience in dogs or man. Our findings with both dyes have given comparable results

1. Haldane, J., and Smith, J. L.: The Mass and Oxygen Capacity of the Blood in Man, J. Physiol. **25**:331-343, 1900.

2. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547-576 (Oct.) 1915.

3. Rasmussen, A., and Rasmussen, G. B.: The Volume of the Blood During Hibernation and Other Periods of the Year in the Woodchuck (Marmota Monax), Am. J. Physiol. **44**:132-148, 1917.

4. Harris, D. T.: The Value of the Vital-Red Method as a Clinical Means for the Estimation of the Volume of the Blood, Brit. J. Exper. Path. **1**:142-158, 1920.

well within the possible errors inherent in the method itself. Table 1 shows these comparable results, employing both dyes, in two normal dogs and two patients with mild chronic arthritis. Hematocrit determinations were made by centrifuging 15 c.c. of blood in calibrated centrifuge tubes for twenty minutes at the rate of 3,000 revolutions a minute. One hundredth of a gram of dry sodium oxalate was used to prevent clotting. The hemoglobin content was estimated according to the Palmer [5] modification of the Haldane carbon monoxid method. The surface area of these patients was computed from the height and weight formula of Du Bois.[6]

REDUCTION OF WEIGHT

A fairly standardized regimen for reducing weight was used in this series of patients. Average diets of 1,200 calories were given, and

TABLE 1.—*Plasma and Total Blood Volume Estimations by Vital Red and Congo Red Methods*

	Date	Dye Used	Weight, Kg.	Plasma Volume, C.c.	Plasma Volume, C.c. for Each Kg.	Blood Volume, C.c.	Blood Volume, C.c. for Each Kg.
Dog B....	1/15/21	Congo red	8.6	470	54.6	885	103.0
	1/27/21	Vital red	...	480	....	800	.....
	2/11/21	Vital red	8.0	440	55.0	770	96.5
	2/14/21	Congo red	7.8	495	63.6	850	108.8
Dog W....	2/ 3/21	Congo red	9.7	490	50.3	855	88.0
	2/11/21	Vital red	8.6	440	51.4	760	87.0
	2/14/21	Congo red	7.9	450	55.7	760	96.0
A426051....	5/26/23	Congo red	73.0	3,325	45.0	5,750	78.0
	5/29/23	Vital red	73.0	3,390	46.0	5,655	77.0
A426243....	6/ 6/23	Congo red	62.0	3,725	60.0	5,825	94.0
	6/ 9/23	Vital red	60.0	3,725	62.0	5,825	97.0

fluids were restricted to 1,500 c.c. Moderate exercise was taken in the form of walking one or two miles daily. Desiccated thyroid was given by mouth in sufficient dosage to elevate and maintain the metabolic rate at from 20 to 25 per cent. above normal for from five to ten days. At this level toxic symptoms were absent or slight. From one to three courses of thyroid treatment as noted above were given each month.

RESULTS

The changes in hemoglobin, red blood corpuscle content, plasma and total blood volume following reduction in weight and surface area varied with the individual case. The detailed findings are given in Table 2.

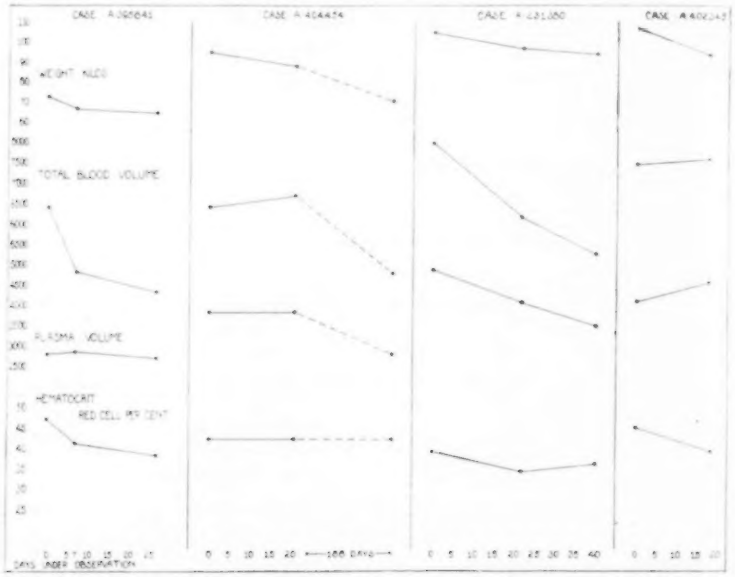
5. Palmer, W. W.: The Colorimetric Determination of Hemoglobin, J. Biol. Chem. **33**:119-126, 1918.

6. Du Bois, D., and Du Bois, E. F.: A Formula to Estimate the Approximate Surface Area if Height and Weight be Known. Clinical Calorimetry, Tenth Paper, Arch. Int. Med. **17**:863-871 (June) 1916.

TABLE 2.—*Blood Values During Weight Loss (Observations on Fourteen Patients)*

Case	Date	Sex and Age	Weight, Kg.	Loss of Wt., Kg	Height, Cm.	Surface Area, Sq. M.	Hemoglobin, per Cent.	Hematocrit Erythrocytes, per Cent.	Plasma Volume			Whole Blood			Clinical Diagnosis
									Total, C.c.	C.c. for Each Kg.	C.c. for Each Sq. M.	Total, C.c.	C.c. for Each Kg.	C.c. for Each Sq. M.	
1 (A388586)	5/10/22	F	106	..	162	2.07	82	36	3,750	35	1,810	5,860	55	2,835	Obesity, mild chronic arthritis
	5/29/22	49	100	6	...	2.02	88	34	4,185	42	2,070	6,340	63	3,130	
2 (A390802)	5/15/22	F	99	..	167	2.08	110	46	3,620	36	1,740	6,700	67	3 220	Obesity, mild chronic arthritis, mild hypertension
	6/12/22	55	93	6	...	2.0	103	39	3,710	40	1,855	6,085	65	3,040	
3 (A392906)	5/31/22	M	115	..	178	2.38	104	41	4,445	38	1,865	7,530	64	2,515	Obesity, myocardial degeneration, arteriosclerosis; edema 1 on admission; 6/5/22: phlebotomy 600 c.c.
	6/ 2/22	65	111	..	...	2.3	...	42	4,500	41	1,950	7,760	70	3,350	
	6/ 8/22	..	105	10	...	2.25	108	41	3,915	37	1,740	6,735	63	3,045	
4 (A270002)	6/ 5/22	M	104	..	167	2.1	108	39	3,955	38	1,880	6,485	62	3,085	Obesity, myocardial degeneration, hypertension; edema 1 on admission
	6/17/22	39	97	7	...	2.04	...	39	4,800	49	2,350	7,870	81	3,830	
5 (A402345)	8/25/22	F	105	..	170	1.85	107	45	4,000	39	2,210	7,435	70	4 020	Obesity, migraine
	9/12/22	44	93	12	...	1.76	103	39	4,555	49	2,585	7,565	81	4,300	
6 (A403665)	9/14/22	F	87	..	157	1.86	101	43	3,365	38	1,810	5,900	67	3,170	Obesity, hypertension, arteriosclerosis
	9/27/22	55	83	4	..	1.81	...	36	3,790	45	2,935	5,905	71	3,255	
7 (A395124)	6/23/22	M	96	..	172	2.08	100	47	3,365	35	1,610	6,345	66	3,050	Obesity, cholecystitis
	7/10/22	48	88	..	...	2.0	...	41	4,138	47	2,070	7,015	80	3,555	
	7/18/22	..	84	12	...	1.97	...	39	4,135	49	2,100	6,700	79	3,400	
8 (A396841)	7/ 5/22	F	72	..	147	1.64	129	47	2,770	38	1,670	5,900	82	3,600	Acute obesity, ovarian disfunction
	7/12/22	30	66	..	...	1.59	...	41	2,835	43	1,785	4,810	73	3,025	
	8/ 2/22	..	64	8	...	1.56	108	38	2,695	41	1,710	4,300	67	2,750	
9 (A400920)	8/17/22	F	111	..	155	2.10	105	44	4,045	36	1,920	7,220	65	3,439	Obesity, hypertension
	9/ 1/22	52	96	15	...	1.96	107	39	4,090	42	2,085	6,705	70	3,500	
10 (A401795)	8/21/22	F	81	..	158	1.8	98	40	3,960	48	2,200	6,710	82	3,730	Obesity, chronic arthritis, mild diabetes
	8/31/22	45	74	7	...	1.74	100	39	3,635	49	2,090	5,960	80	3,430	
11 (A404454)	9/19/22	F	94	..	172	2.06	111	42	3,870	41	1,880	6,450	68	3,130	Obesity, mild hypertension, cholecystitis (?)
	10/10/22	41	87	7	...	1.99	106	42	3,830	44	1,925	6,690	77	3,320	
	4/18/23	..	70	24	...	1.84	118	42	2,770	40	1,500	4,775	68	2,600	
12 (A393595)	6/10/22	M	115	..	172	2.26	116	40	4,805	42	2,110	8,105	70	3,585	Obesity
	6/26/22	52	106	9	...	2.16	...	40	4,615	43	2,045	7,675	72	3,500	
13 (A164776)	5/17/23	F	140	..	158	2.35	111	41	3,850	27.5	1,640	6,500	47	2,765	Obesity, hypertension
	5/31/23	53	134	6	...	2.26	111	42	3,845	28.7	1,700	6,625	50	2,930	
14 (A231380)	5/30/22	M	104	..	178	2.2	94	39	4,805	47	2,220	7,975	77	3,625	Typhoid fever, obesity
	6/22/22	40	96	..	...	2.12	...	34	4,045	42	1,910	6,130	64	2,890	
	7/10/22	..	93	11	...	2.10	...	36	3,440	37	1,670	5,372	58	2,560	

Percentage of Hemoglobin and Red Blood Corpuscles (Hematocrit).—The initial determinations for hemoglobin varied from 82 to 129 per cent. and for red blood corpuscles, from 36 to 47 per cent. These findings fall within the normal range for both sexes between 30 and 65 years of age. In six of the present series of cases (Cases 2, 5, 6, 7, 8 and 14) there was a distinct, though not marked, fall in the hemoglobin or red blood corpuscle percentage, or in both, following loss of body weight. In the first four of the foregoing cases there was no other evidence of a developing anemia. The patient in Case 14 passed



Four types of variations in blood and plasma volumes during weight reduction.

through the typical course of typhoid fever, which might account for a mild degree of secondary anemia. In Case 8 the fall in hemoglobin from 129 to 108 per cent. was accompanied by a decrease in the total number of circulating red blood corpuscles; this was probably a true anemia as there was no change in the plasma volume. In the remaining eight cases there were no noticeable changes from the initial determinations.

Plasma Volume.—The initial determinations were relatively lower than normal when compared to body weight. In normal persons, the variation is from 42 to 54 c.c. for each kilogram; in these cases it was

from 27.5 to 48 c.c. However, when compared with surface area, the initial plasma volume showed little change from normal.

In Cases 1, 4, 5, 6 and 7, following a reduction in weight of from 4 to 12 kg., there was a definite rise in the total and relative amounts of plasma volume. The relative increase applied to both weight and surface area. In Cases 1 and 4, there was no associated change in percentage of red blood corpuscles, while in three (Cases 5, 6 and 7), there was a measurable fall without other evidences of anemia.

A marked fall (28 to 29 per cent.) in total plasma volume occurred in Cases 11 and 14. The histories of these patients are of striking interest. In Case 14, the patient entered the hospital with typhoid fever, which ran a typical course without complications. He lost 11 kg. in weight. Blood examination on three occasions at intervals of three weeks showed a steady decrease in total plasma, amounting in all to 1,424 c.c., or 29 per cent., and accompanied by a small decrease in the percentage of red blood corpuscles (from 39 to 36 per cent.). The relative decrease in plasma was from 47 to 37 c.c. for each kg., and from 2,215 to 1,670 c.c. for each square meter. In Case 11, the patient lost 7 kg. in three weeks, and 24 kg. in seven months under strict treatment for obesity. This marked loss in weight was accompanied by a decrease of 1,100 c.c., or 28 per cent., in total plasma. The relation of total plasma to body weight, 42 c.c. for each kilogram, remained unchanged, but there was a definite decrease in the relative amount of plasma to surface area. There was no striking loss of hemoglobin or change in red blood corpuscle percentage.

In six of the seven remaining cases in which the loss of weight was from 6 to 15 kg., the changes in total and relative plasma volume were small.

Blood Volume.—The initial determinations in all but three cases showed a reduced blood volume when compared to body weight. In these exceptions (Cases 8, 10 and 14), the findings were from 77 to 83 c.c. for each kilogram, coming within the range of the normal variation of from 74 to 99 c.c. for each kilogram. The variations in the relationship of blood volume to surface area are greater in obese persons than in normal subjects. The former vary from 2,515 to 3,730 c.c. for each square meter, and the latter from 2,790 to 3,460 c.c. for each square meter. The results of total blood volume estimations were more variable when compared with loss of weight than those of plasma.

Three patients (Cases 1, 4 and 7), after the loss of weight, had an increase in total and relative blood volume, and this was always associated with an increase in the total and relative amount of plasma. The red blood corpuscle percentage did not change in Cases 1 and 4; in Case 7 there was a definite decrease. In Cases 2, 3, 8, 9, 10, 11 and

14, there was a demonstrable decrease in total blood volume, accompanied by no change or a slight fall in the percentage of red blood corpuscles. In five of these (Cases 2, 3, 9, 10 and 11), this decrease in total blood volume was not accompanied by a relative parallel decrease in relation to body weight and surface area. On the contrary, in two, a decrease was found. The latter cases (Cases 14 and 8) were striking on account of a marked fall of from 28 to 29 per cent. in blood volume. This decrease was due to a loss of both plasma and red cells in Case 14, while in Case 8 the loss was demonstrable in the red cells only.

In Cases 12 and 13, there was practically no change in total or relative amounts of blood volume. Plasma determinations also showed no change. Both patients lost relatively little weight while under observation.

COMMENT

Loss of weight in this series of obese subjects did not occasion constant changes in blood and plasma volume, or in the percentage of hemoglobin or red blood corpuscles. Four types of blood changes are shown in the chart. In Cases 5, 6 and 7 there was an increase in total plasma, a decrease in the percentage of red blood corpuscles and little or no change in total blood volume. The increase in circulating plasma may be related to the therapeutic use of thyroid extract. In only two cases (Cases 14 and 11) was there a marked decrease in total plasma. In Case 14, typhoid fever was present, and in Case 11, the loss of weight amounted to 24 kg. Loss of plasma in typhoid fever suggests that there may be a similar loss of plasma in other acute febrile diseases. In Case 11, the loss of plasma varied directly with the loss of weight, so that the initial relationship between body weight, total plasma and total blood remained constant: 42 and 68 c.c. for each kilogram. If a low relative blood and plasma volume is always found in obese persons, as our results show, then the determinations in Case 11 indicate that even at the reduced weight of 70 kg. the patient had an abnormal amount of adipose tissue.

The total circulating blood was increased in two cases, suggesting that loss of weight may have opened up resting capillaries and thus increased the amount of blood in circulation. In Case 4, the early disappearance of a slight edema may have been a factor in causing an increase in circulating blood volume. The marked decrease in blood volume that occurred in Cases 8 and 14 is of special interest. In Case 8, in which marked obesity developed in six months, the decrease was due to a loss or possible redistribution of red blood corpuscles, as no change was found in the amount of circulating plasma. The fall in red blood corpuscles and hemoglobin percentage strongly indicates that red blood cell destruction had occurred. There were no other clinical

facts indicative of anemia. On the other hand, in Case 14 the red blood corpuscle percentage and total circulating blood volume were decreased, as well as the total plasma. The anemia which occurs in typhoid fever may explain the red cell loss, while the loss of plasma was possibly associated with the excessive protein catabolism present in this disease.

SUMMARY

1. The circulating blood and plasma volumes when compared to body weight are smaller in obese than in normal persons.

2. Loss of weight in obese subjects, as brought about in this series of cases, did not result in constant changes in blood and plasma volume or in the percentage of hemoglobin or red blood corpuscles (hematocrit).

3. In three cases, following loss of weight there was evidence of blood dilution, but no definite evidence of anemia.

4. A decrease or increase of total circulating blood volume may occur with reduction in weight. In this series, when a marked decrease occurred, there was evidence of anemia.

MERCURIC CHLORID POISONING*

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The most trying group of poisoned patients encountered at a general hospital is the group that has taken mercuric chlorid. It is taken with suicidal intent in over 90 per cent. of the instances, and the vast majority of the group are young women. The accidental poisonings are infrequent, and occur when a tablet is taken by mistake for a coal tar or other preparation. Occasionally, the patient who has used the solid tablet in the vagina will present herself. Once a child who had swallowed the mercury from a broken thermometer came under treatment. For the most part, the poison is taken by mouth, usually by swallowing the tablets, and occasionally by dissolving them in water before swallowing. One patient ate some diluted mercurial ointment, and another drank a 1 : 10 mercuric chlorid solution which she obtained in a hospital.

When the mercury, even in tablet form, enters the stomach, the poison is quickly taken up, and in experimental animals (dogs) the mercury has been detected in the blood three minutes after a tablet was placed in the animal's stomach.[1] This occurred when the dose of mercuric chlorid was 0.5 gm. per kilogram of body weight. In doses as small as 0.024 gm. per kilogram, mercury has been found in the blood ten minutes after the tablet was placed in the stomach. As soon as the mercuric chlorid gets into the circulation, various pathologic changes occur rapidly. As shown by Burmeister and McNally, these changes are degenerative in character, and, if continued, lead to individual cell death. The kidney is especially affected, and these changes occur simultaneously with the presence of mercury in the circulating blood. They found that in massive intoxications the immediate renal changes will vary with the size of the dose, while in smaller doses, the renal changes will vary with the duration of the intoxication. Though the brunt of the intoxication seems to be borne by the kidney and liver, it is shown that the entire body suffers from the metal injury. Rosenbloom,[2] in a study of a fatal case of mercury poisoning, found mercury in practically every organ of the body, including the bones and central nervous system.

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1. Burmeister, W. H., and McNally, W. D.: Mercury Poisoning, J. M. Res. **36**:87 (March) 1917.

2. Rosenbloom, J.: A Note on the Distribution of Mercury in the Body in a Case of Acute Bichloride of Mercury Poisoning, J. Biol. Chem. **20**:123, 1915.

When death occurs, it is usually the result of the kidney injury. MacNider,[3] who has studied the action of mercury on dogs, found that in the acute mercuric chlorid intoxications death occurred, due either to the shock associated with the severe mercury enteritis, or to a delayed kidney injury; that the injury to the kidney has been constantly associated with the development of an acid intoxication, and that the delayed kidney injury is not due to the action of the mercury as such during its elimination by this organ. MacNider [4] has also demonstrated experimentally that poisoning by uranium, another heavy metal, is associated with the development of organic acids, such as diacetic acid and acetone.

The kidney changes are those of an acute nephritis; there usually develops a pale, swollen kidney, perhaps with hemorrhagic areas, mostly glomerular in the more severe intoxications. Menten,[5] in a series of experiments on rabbits, found that in animals that received above 0.005 gm. per kilogram, gross pathologic changes could be detected in the kidney in a short time. If the dose of mercuric chlorid was much smaller, for instance, 0.0012 gm. per kilogram, given intravenously, microscopic changes indicating kidney injury could be detected within five minutes after the injections. These changes were well defined and could be found in the liver as well as in the kidney. The experimental doses of the poison were smaller when compared with the lethal dose of 0.004 gm. per kilogram, as found by Barbour.[6] In one or our patients who died within nineteen hours after taking 0.03 gm. per kilogram, the liver showed marked edema with but slight edema of the kidneys. In another patient who died seven days after she took a similar dose necropsy revealed the most marked acute changes in the kidneys, though the liver was severely injured.

In common with others,[7] we have found certain constant changes in the blood chemical studies on animals and patients. There is a retention of the nitrogenous elements, such as urea nitrogen, uric acid and creatinin, depending on the extent of the body injury, especially that of the kidney. Acid intoxication, as evidenced by a reduction of the alkali reserve, is one of the most frequent findings. There is also a diminution of the concentration of the whole blood chlorids. With the improvement in the patient, the nitrogen elements of the blood return to normal, together with the alkali reserve and the whole blood chlorid concentra-

3. MacNider, W. D.: A Study of Acute Mercuric Chloride Intoxication in the Dog, with Special Reference to the Kidney Injury, J. Exper. Med. **27**:519 (April) 1918.

4. MacNider, W. D.: Uranium Poisoning, J. Exper. Med. **26**:1, 19 (July) 1917.

5. Menten, M. L.: J. M. Research **43**:315 (June-July) 1922.

6. Barbour, H. G.: Mercuric Chlorid Poisoning in Animals Treated Unsuccessfully by Parenteral Administration of Hall's New Antidote, J. A. M. A. **64**:736 (Feb. 27) 1915.

7. Killian, J. A.: J. Lab. & Clin. Med. **7**:129 (Dec.) 1921.

tion. In severe intoxications, the phenolsulphonephthalein output is greatly lowered, not infrequently to zero. With the improvement of the patient, the output gradually rises. In several of the patients studied who had a complete anuria for a day or more and in whom the kidney functional test did not show any excretion of the dye in two hours, there was a steady rise of the phenolsulphonephthalein output with the improvement in the patient's condition. In one patient the output gradually rose to 66 per cent. on the thirty-third day of the disease, after a complete anuria for three days and a severe oliguria for the following two. There is a moderate increase in the white cell count, to as high as 20,000 or more, with an increase in polymorphonuclears. A few days after the poison is taken, this increased white cell count gradually diminishes as the patient improves, or it may remain increased until death.

The urinary findings are significant. Albumin appears early, often several hours after the patient has taken the poison. Soon there is a diminution in quantity of urine, which is often the forerunner of a complete anuria. As the quantity of urine secreted diminishes, the organic elements increase, and all forms of casts and many blood and pus cells are frequently found. In patients with severe intoxications, the urine is often bloody. One of the most constant findings has been that the urine is highly acid to methyl red. As the intoxication progresses, all signs of uremia may be present. Headaches, coma and convulsions are not infrequent in this type. In several of our patients, a generalized edema occurred. In one patient with a total suppression of urine for three days, followed by two days when he voided only a few ounces each day, a generalized rather severe edema developed. The edema of the eyelids was sufficient to obstruct his vision. The entire face, neck and extremities were puffy, and a moderate amount of ascites was present. This edema rapidly subsided as soon as the patient commenced to void. In one of the fatal cases, in a patient who lived twenty-one days after she was poisoned, there developed marked enlargement of the submaxillary glands, herpes of the lips, pleurisy and finally terminal pneumonia.

The diagnosis of mercury poisoning is not difficult. The patient usually gives a clear history of taking poison. The characteristic symptoms with the urinary findings are almost constant. In practically all of the patients that came under observation, the vomitus, urine or feces was examined for mercury by the method of Vogel and Lee.[8] Metal has been found in the urine within fifteen hours after ingestion, but it usually does not appear in the feces before from thirty to forty

8. Vogel, K. M., and Lee, O. I.: Detection of Mercury in the Excretions, J. A. M. A. **62**:532 (Feb. 14) 1914.

hours. Most of it is excreted by the bowel, and can usually be detected for from seven to ten days, though in a few patients it has been found many days later.

TREATMENT OF MERCURIC CHLORID POISONING

The treatment of this intoxication presents itself as a difficult problem. In the last decade many so-called specifics have been presented. For several of them claims are made that the mercury is placed in combination with the therapeutic agent, thereby producing a nontoxic substance which subsequently can be eliminated. If the pathology of this intoxication is understood, it is evident that pathologic changes take place rapidly, depending on the severity of the irritation. The problem then is how to overcome the effects of the poison. The familiar cloudy swelling and later degenerative changes in the kidney are merely an example of the changes that have taken place throughout the entire body. If the process continues, cell death and necrosis follow, and the organism succumbs to a generalized intoxication. Knowing this, we believe that it is useless to attempt to counteract the metallic poison itself, but that our efforts should be directed toward preventing the irreparable pathologic changes that will occur if the intoxication is not combated. The cloudy swelling, nephritis and uremia are associated with an increase in the production of acid bodies. Fischer [9] shows that these changes are due to the acidosis. MacNider [3] found this acid intoxication always associated with mercury poisoning. With another heavy metal (uranium) poisoning, he found that organic acids were produced by the intoxication, and that the administration of an alkali (sodium bicarbonate) lessened the toxicity of the uranium by delaying the formation of organic acids.

The logical treatment, then, seems to be to attempt to counteract any pathologic changes that have occurred; to prevent the progress of the pathologic changes, and, finally, to eliminate the toxic material as soon as possible.

The treatment developed attempts to carry out that program, and, when compared with other methods of treatment, it has been fairly successful.

The treatment is divided into several stages. As soon as the patient comes under observation—the sooner the better—a stomach tube is introduced, and the stomach is washed with 2 quarts (liters) of a saturated solution of sodium bicarbonate. This is continued until the washings return clear. Before the tube is removed, 6 ounces (178 c.c.) of a saturated solution of magnesium sulphate is allowed to remain in

9. Fischer, M. H.: Edema and Nephritis, New York, John Wiley & Sons, 1915.

the stomach. A soapsuds enema is then given. Most of the patients vomit soon after taking the poison, and probably some of the mercury is eliminated in this way.

To introduce alkali into the system, patients should receive an intravenous injection of alkali as soon after the preliminary treatment as possible. The preparation that we have used is Fischer's solution. This solution consists of crystallized sodium carbonate (Na_2CO_3.-10 H_2O), 10 gm., and sodium chlorid, 15 gm., both dissolved in 1,000 c.c. of distilled water. If this is not available, a solution of 4 per cent. sodium bicarbonate may be used. In patients who have not any abnormality of the circulatory system, from 1 to 1.5 liters can be tolerated without any difficulty. In patients who have taken large amounts of poison, we have given as high as 1,800 c.c. at the first injection. The alkaline therapy is continued by mouth. We have used a modification of the old "potus imperialis" by dissolving 4 gm. (1 teaspoonful) of potassium bitartrate and 2 gm. (½ teaspoonful) of sodium citrate in a glass of water, orangeade or lemonade. The patient receives 8 ounces (236 c.c.) of this drink from six to eight times a day, from the onset. We have rarely used rectal administration of alkali in water on account of the irritation of the lower bowel associated with the bloody diarrhea. Hot packs have not been used except in the few patients who had a complete suppression. A liberal diet is allowed, including meat, after the diarrhea ceases.

The treatment is controlled by urinalysis. We endeavor to make the urine alkaline to methyl red, and keep it so. Fischer has demonstrated that in patients with disease of the kidneys, the urine of whom cannot be kept alkaline to methyl red, the disease may progress and often lead to complete suppression. Under this treatment the patient usually voids large quantities of urine. Albumin, casts and blood are usually present for several days, and gradually diminish until the urine becomes clear. Most of the patients under observation showed a normal urine from the tenth to the fourteenth day after taking the poison. If the patient has taken over 7 grains (0.46 gm.) of mercuric chlorid, and shows marked urinary disturbance, a second, and at times a third, intravenous injection of Fischer's solution is given. The injections are given on successive days.

Previously [10] I have reported the results of this treatment in several groups of patients. At the present time, I can report the entire series of 135 consecutive patients poisoned by some form of mercury with

10. Weiss, H. B.: A Method of Treatment of Mercuric Chlorid Poisoning, J. A. M. A. **68**:1618 (June 2) 1917; The Treatment of Bichloride of Mercury Poisoning, Ohio State M. J. **13**:595 (Sept.) 1917; The Principles of Treatment in Mercuric Chlorid Poisoning, with Results of Treatment, J. A. M. A. **71**:1045 (Sept. 28) 1918.

only eight deaths, a mortality of less than 6 per cent. These patients took from 1½ to 50 grains (0.09 to 3.25 gm.) of mercuric chlorid, usually in tablet form, or similar amounts by drinking a prepared solution or eating mercuric ointment. In only fifteen patients did a complete suppression develop. Of these, seven died; and in the other eight patients the secretion of urine was established, and the patients recovered. The patients who had the most difficulty were of the group that took over 30 grains (1.95 gm.) of mercuric chlorid, and those in whom the institution of treatment was delayed.

The vast majority of the patients placed on this treatment do not develop evidence of serious kidney disease except for a moderate albuminuria, which rapidly clears. A free secretion of urine is maintained. The patient usually makes a clinical recovery in from twelve to fifteen days. Examination of several of these patients a year after they were poisoned and treated did not show any abnormality that could be connected with the poisoning.

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INSULIN IN THE SEVERER FORMS OF DIABETES

WITH REPORT OF CASES *

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During the winter of 1922-1923, at St. Luke's Hospital, New York City, we had the opportunity to study the effect of insulin in thirty cases of diabetes, most of them severe. We report in detail thirteen in which the patients have been under long continued treatment.

Our work confirms the reports of the value of insulin in the treatment of diabetes in the publications of Drs. Banting, Best and McCleod, and others of the Toronto group. Our method in general has depended on whether there has been a dangerous amount of acidosis present or not. In cases of coma or severe acidosis insulin was given immediately, and the ordinary methods of treatment, such as forced fluids by mouth or rectum with bicarbonate of soda in addition, were employed. When only a moderate amount or no acidosis was present the patients were, in the earlier cases of our series, rendered sugar free by dietary regulation before initiation of specific therapy. In the former group, immediate examinations of urine, blood sugar and the alkali reserve in the blood by the Van Slyke method were made, and usually a moderate dose of insulin, from 10 to 20 units, was given before the results of the examinations were determined. In these cases, the insulin was given at once, with orange juice or glucose, by mouth, by rectum or intravenously. When patients did not show alarming acidosis an effort was made at the start to render them sugar free on an under-nutrition diet, and later in the series they were placed on a low diet usually containing 50 gm. carbohydrate, 50 gm. protein and, in the absence of acidosis, 50 gm. of fat. The patients were kept on this diet for a period of days until the sugar excretion was practically constant, in order to establish a preliminary period in which a patient's ability to utilize sugar without insulin administration could be determined.

Owing to the fact that the proteolytic ferments of the stomach and pancreas destroy insulin, this drug must be administered hypodermically or intravenously, and it is improbable for this reason that this mode of administration can be changed to the ordinary one by mouth. Insulin must be given with definite relationship to carbohydrate intake, as its action is dependent on having carbohydrate on which to work. Conse-

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quently, we have given it subcutaneously about fifteen minutes before meals with the idea that the absorption of the drug into the circulation and the carbohydrate from the digestive tract would go on at approximately the same time.

Two things are necessary: first, there must be glucose in the circulation on which the insulin may act and thus prevent the development of symptoms of hypoglycemia; second, a sufficient amount of insulin should be given to take care of the carbohydrate, thus keeping the blood sugar below the threshold of excretion. Our ordinary procedure has been to determine the amount of sugar in the urine on constant diet, and to give the amount of insulin that will enable the body to utilize the same. This is no easy matter as the number of grams of carbohydrate made available by a single unit of insulin is variable, depending on the degree of function of the individual pancreas, our low figure being 0.9 gm., and our high figure 2.3 gm. The individual pancreas may vary in its insulin output so that what is true for the patient one day may not be true another day. In general, however, taking an average of 3 gm. per unit and using small doses with low diet to begin with, we have been able to control glycosuria rapidly and to get the patient back on a maintenance diet.

Blood sugar determinations were made on a fasting stomach and at frequent periods after insulin administration. Contrary to the rules obtaining in the ordinary treatment of diabetes, the high figures were invariably fasting, and the low figures were those following meals and insulin administration. Consequently, when the single blood sugar was taken, we made our determinations two hours after lunch. This was done to avoid the dangers of hypoglycemia, several cases of which have been observed by those working with this new agent. The symptoms may vary from hunger, fatigue, sweating, feeling of nervousness or tremor, to convulsions and coma. The more serious symptoms we have not personally observed, although some of our afternoon blood sugar determinations have been as low as 0.05 per cent. These symptoms are speedily removed by the ingestion of carbohydrate, preferably orange juice, or in severer cases by glucose solution given by mouth, rectum or, if necessary, intravenously. All patients discharged on insulin were instructed not only in the technic of calculating and weighing their diets and the analysis of their urine for sugar, but also concerning the possibility of the advent of the symptoms characterizing hypoglycemia and the nature of these symptoms. They were also told to take orange juice if the symptoms were marked. We have not considered it advisable to discard our preconceived notions of the effect of hyperglycemia and its consequent glycosuria in reducing pancreatic

function, as shown by Allen's [1] work on experimental animals; we have, therefore, not left in the urine the "sugar pad" to protect the patient against hypoglycemia from overdosage of insulin. The problem thus resolves itself into keeping the blood sugar below the level of sugar excretion, which Williams states to be on an average 180 mg. per 100 cubic centimeters although individual cases vary widely below and above this figure, and to avoid giving an insulin dosage so great as to produce symptoms of hypoglycemia. In certain instances it may be necessary to respace the insulin dosage, and even to give a small dose in the evening. Our ordinary practice, however, has been to give the largest dose before breakfast when the blood sugar is highest, and approximately equal doses before dinner and supper.

Sugar determinations in the urine have been made by the Benedict-Osterberg method by which sugar is demonstrated in normal urine in amounts varying from 1 gm. or more a day. The alkali reserve is calculated by the Van Slyke method, the total blood sugar by Benedict's method and the total nitrogen by the Kjeldahl method.

The amount of glucose available to the body has been calculated in this series by adding to the carbohydrates of the diet the amount of glucose theoretically available from the protein (58 per cent.). This we have calculated not from the protein of the diet, but by the urinary nitrogen as representing the total amount of protein actually metabolized in the twenty-four hour period. While more accurate than direct calculation from the diet, it is open to the disadvantage that urine collections must be exact. We have also calculated 10 per cent. of the fat as available for the formation of glucose. While the work of Lusk [2] makes it certain that in the absolute diabetic with a dextrose nitrogen ratio of the urine of 3.65 : 1 such metabolism of the protein molecule does take place, it is not experimentally established that this particular utilization of the protein molecule occurs in the normal person or in the person with mild diabetes. The respiratory quotient, however, of the protein fed animal suggests that this is the case. Consequently, we feel it fair to calculate our available glucose as stated above.

CASE 1.—*History*.—A man, aged, 22, single, a clerk, born in the United States, had had diabetes since September, 1922. He was admitted to the hospital on Dec. 11, 1922; he was discharged on March 3, 1923. (He was then followed in the diabetic clinic.) In September, 1922, he had an alveolar abscess which ruptured and continued to discharge for two weeks, at the end of which time the tooth was finally extracted. At about the same time he noticed weakness, lassitude and loss of weight. Examination of the urine revealed sugar in large amount—149 gm. The patient had had malaria in 1918. His family history was negative.

1. Allen, F. M.: Glycosuria and Diabetes, Cambridge, Harvard University Press, 1913.
2. Lusk, G.: Elements of the Science of Nutrition, Philadelphia, W. B. Saunders Company, 1919.

Physical Examination.—Examination revealed marked undernutrition; it was otherwise negative. The patient weighed 102 pounds (46.26 kg.). Sugar utilization: In the preliminary period after the administration of sugar the plus balance was 6.

During February the utilization per insulin unit was 16; last week observed utilization per insulin unit was 23.3.

Treatment and Course.—On the first day of admission to the hospital he was put on a diet of carbohydrate, 50 gm.; protein, 25 gm.; fat, 20 gm.; and on this diet excreted 149 gm. of sugar. For the next week an effort was successfully made to render him sugar free by undernutrition with four starvation days, yet during the first four days he showed sugar in his urine derived entirely from body protein, if we except the possibility that the excretion of the first day or two represents glucose previously ingested. On the ninth day, he was given 9 units of insulin and a diet of carbohydrate, 50 gm.; protein, 50 gm.; fat, 50 gm. He remained sugar free from that time on a diet gradually increased to from 600 to 5000 calories with 200 gm. of available glucose on the same insulin dosage. The blood sugar remained between 95 and 125 mg. Fatigue and lassitude disappeared when a maintenance diet was attained. His weight increased from 100 to 122 pounds (45.35 to 55.33 kg.), and for the past two months he has resumed his work, weighing his food, analyzing his urine and administering insulin to himself.

Comment.—We have here the problem of an absolute diabetic, certainly so when first observed, his diet for the first day furnishing a possible 64 gm. of sugar, while the excretion was 149 gm., the excess of nitrogen of urine over nitrogen of food being 6.7 gm. We can thus assign 64 gm. of sugar to his diet, 25 gm. as derived from destruction of body protein (a loss of 41.8 gm.), while the remaining 60 gm. represent carbohydrate previously ingested. Not until the fifth day did the dextrose nitrogen ratio of the urine reach 2:1, the urinary sugar still being derived in part from body protein. Yet this patient five months later was able to utilize 220 gm. of sugar on 9 units of insulin or, if we calculate in the ordinary way, of sugar utilizable before and after insulin, 23.3 gm. per unit. Does this figure represent the truth, or has a restoration of pancreatic function taken place? The latter seems far more probable than that the insulin unit has been able to cause directly the burning of such increasing amounts of carbohydrate. In no other case in the series has the pancreatic function thus increased. The history too is significant, as symptomatic diabetes followed a tooth infection of severe nature, and it is probable that the pancreatic function if previously impaired was much damaged by the infection.

A complete laboratory report of this case, during the patient's stay in the hospital, is given below, in addition to the graphic charts (Figs. 1, 2, 3 and 4).

Case 2.—*History.*—A man, aged 20, single, a chauffeur, born in the United States, had had diabetes for one and one half years. He was admitted to the hospital on March 22, 1923. He said he thought diabetes followed an automobile accident. On January 23, he consulted a physician because he was

Laboratory Report in Case 1

Date	Urine, 24 Hrs., C.c.	Ht. / Wt.	Food				Urine							Blood		Miscellaneous				Units Insulin
			Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Total Calories	Specific Gravity	Reaction	Albumin	Ferric Chloride	Nitroprussid	Sugar per Cent.	Total Sugar Gm.	Sugar Mg.	Carbon Dioxid, % by Volume	Total Nitrogen	Nitrogen of Food	Glucose Available	Glucose Utilized	
12/18/22	2,400	100	100	100	100	1,700	1.030	Acid	v.ft.	+	++	2	4.80	.....	.. .	....	..	.....	.....	..
12/19/22	2,650	...	50	50	70	1,050	1.019	Acid	v.ft.	+++	++++	5.62	149.0	232 a.m.	.. .	12.0	8.0	101.6	—47.4	..
12/20/22	2,650	102	50	25	20	480	1.014	Acid	v.ft.	++	+++	5.62	149.0	200 a.m.	....	10.7	4.0	91.54	—57.46	..
12/21/22	2,650	102	25	25	5	200	1.012	Acid	v.ft.	+++	++++	3	79.5	188 a.m. 222 a.m.	52.8	12.2	4.0	69.59	—9.91	..
12/22/22	2,550	100	0	0	0	.....	1.008	Acid	v.ft.	++	++++	2	51.0	188 a.m.	....	8.92	0	32.56	—18.44	..
12/23/22	.....	100	0	0	0	.....	1.010	Acid	0	+	+	ft.	.....	185 a.m	50	...	0	.....	.....	..
12/24/22	2,400	100	0	0	0	.....	1.005	Acid	0	+	++	0.0372	8.9	125 a.m	. . .	4.4	0	16.06	+7.16	..
Week ending 12/24/22	.....	...	...	...	...	.....	. ..	. .	...	....	.....	.....	.....	.....	....	. ..	....	.....	.....	..
12/25/22	2,300	102	25	25	0	200	1.007	Acid	v.ft.	++	++	0.0357	7.85	143 a.m. 1428 p.m.	51	7.5	4.0	52.37	44.52	..
12/26/22	1,800	...	25	25	0	200	1.005	Acid	v.ft.	++	++	0.0375	6.75	134 p.m	. . .	10.3	4.0	62.59	55.84	..
12/27/22	1,750	102	25	25	0	200	1.007	Acid	v.ft.	+	++	0.5	8.75	200 a.m	50.4	6.5	4.0	48.72	39.97	..
12/28/22	2,500	105	0	0	0	.....	1.003	Acid	v.ft.	+	0	0.045	1.12	154 a.m.	....	6.3	0	22.99	21.87	..
12/29/22	1,700	105½	35	35	35	595	1.005	Acid	v.ft.	+	0	0.075	1.28	105 a.m. 87 p.m.	. . .	6.1	5.8	58.76	57.48	9
12/30/22	1,900	108½	35	35	35	595	....	.....	...	....	....	.....	.....	118 a.m 134 p.m	. . .	....	5.8	.....	.....	9
12/31/22	2,000	110	50	50	50	950	1.006	Acid	v.ft.	+	0	0.085	2.46	869 p.m	. .	9.8	8	90.77	88.31	9
Week ending 12/31/22	.....	...	...	...	...	.....	....	....	...	. ..	....	.....	.....	.... . .	.. .	7.7	4.5	... ..	.....	27
1/ 1/23	3,150	108	50	50	50	950	1.005	Alkaline	v ft.	+	0	0.034	1.07	105 a.m 130 p.m	. . .	8.8	8	87 12	86.05	9
1/ 2/23	2,300	108	50	50	50	950	1.003	Acid	v.ft.	v.ft.	0	0.068	1.6	105 p.m.	. .	5.95	8	77.71	76.11	9
1/ 3/23	2,200	110	50	50	60	1,040	1.007	Acid	v.ft.	0	0	0.056	1.23	125 p.m.	. .	6.45	8	79.54	78.31	9
1/ 4/23	3,100	110	50	50	70	1,026	1.003	Acid	v ft.	0	0	0.031	0.96	125 p.m	. .	8.15	8	86.74	85.78	9
1/ 5/23	3,250	108½	50	60	80	1,254	1.003	Acid	v.ft.	+	0	0.075	2.43	95 p.m	.	8.2	9.6	87.93	85.50	9
1/ 6/23	.....	108½	50	60	80	.....	1.015	Acid	0	0	0	.....	0	74 p.m	. . .	....	....	.....	.....	9
1/ 7/23	3,150	108½	50	60	80	1,160	1.005	. . .	v.ft	0	+	0.062	1.95	109 p.m.	....	9.1	9.7	91.21	90.26	9
Week ending 1/ 7/23	.. ..	...	...	. .	...	.....	. . .	.. .	.	.	.....	.....	.....	.... .	.. .	7.7	8.5	... ..	.....	27
1/ 8/23	2,600	108	50	70	90	1,290	1.007	.. ..	v.ft	0	0	0.050	1.3	105 p.m	. . .	8.2	10	88.93	87.63	9
1/ 9/23	2,350	108	60	75	100	1,453	1.008	. .	v.ft.	0	0	0.027	0.63	105 p.m	. . .	8.2	12.2	99.93	99.30	9
1/10/23	2,400	107	60	75	100	1,449	1.007	.. .	v.ft.	+	0	0.027	0.91	100 p.m	. . .	11.3	12.4	111.24	110.33	12
1/11/23	3,650	105½	60	75	100	1,446	1.006	. ..	v.ft.	0	0	0.022	0.81	95 a.m. 87 p.m	. . .	10	12.08	106.50	105.69	12
1/12/23	3,750	104	60	75	130	1,710	1.007	. ..	v.ft.	0	0	0.026	0.925	.....	....	12.6	12	118.99	118.07	12
1/13/23	.....	103	60	75	130	.....	1.010	. ..	0	0	+	0	.....	125 p.m	. . .	...	...	.....	.....	12
1/14/23	2,000	103	60	75	130	1,710	1.009	. ..	v.ft.	0	+	0.024	0.48	.....	.. .	7.1	12	98.91	98.43	12
Week ending 1/14/23	.....	...	...	...	...	.....		...		...	.. ..	.....	.....	.....	...	9.56	11.7	.....	.....	78
1/15/23	2,600	103	60	75	130	1,710	1.008	.. ..	0	0	v.ft	0.035	0.91	....	. . .	10.5	12	111.31	110.41	12
1/16/23	2,300	105	60	75	130	1,710	1.008	.....	0	0	+	0.023	0.53	.....	.. .	7 4	12	100.01	99.48	12
1/17/23	2,500	105	65	85	140	1,860	1.012	.. .	v.ft.	0	+	0.06	0.75	137 p.m	. . .	9.05	13.6	112.03	111.28	12
1/18/23	3,000	105	65	85	140	1,860	1.006	. .	v.ft.	0	0	0.024	0.86	.....	....	11.4	13.6	120.61	119.75	12
1/19/23	2,500	104	65	85	140	1,860	1.008	....	v.ft.	0	+	0.021	0.52	118 p.m.	. . .	10.3	13.6	116.59	116.07	12

1/16/23	2,300	105	60	75	120	1,770	1.010	.....	v.ft.	0	+	0.03	0.75	137 p.m.	....	9.06	13.6	.....	.....	12
1/17/23	2,500	105	65	85	140	1,860	1.012	.....	v.ft.	0	0	0.024	0.86	.....	....	11.4	13.6	130.61	119.75	12
1/18/23	2,600	105	65	85	140	1,860	1.006	.....	v.ft.	0	+	0.021	0.52	118 p.m.	....	10.3	13.6	116.59	116.07	12
1/19/23	2,500	104	65	85	140	1,860	1.008	.....	v.ft.	0	+	0.021	0.52	118 p.m.	....	10.3	13.6	116.59	116.07	12

1/20/23	2,300	104	65	85	140	1,860	1.010	.....	0	0	0	0	.....	.....	....	....	13.6	.....	.....	12
1/21/23	2,500	104	65	85	140	1,860	1.004	.....	v.ft.	0	0	0.048	1.2	.....	....	8.9	13.6	111.48	110.28	9
Week ending 1/21/23	.....	...	...	...	...	.....	.....	.....	...	....	....	.....	.....	.....	....	9.6	13.1	.....	.....	81
1/22/23	2,600	104	65	85	140	1,860	1.009	.....	v.ft.	0	0	0.037	0.96	.....	....	9.6	13.6	114.64	113.08	9
1/23/23	2,600	104	70	95	160	2,096	1.010	.....	v.ft.	0	0	0.032	0.83	.....	....	10.05	15.18	122.56	121.67	9
1/24/23	2,500	105	70	95	160	2,096	1.008	.....	v.ft.	0	0	0.031	0.775	143 p.m.	....	7.55	15.1	113.55	112.78	9
1/25/23	2,600	106	70	95	160	2,096	1.010	.....	v.ft.	0	0	0.039	0.94	.....	....	6.55	15.1	109.90	108.96	9
1/26/23	2,600	106	70	95	160	2,096	1.008	.....	v.ft.	0	0	0.033	0.86	.....	....	10.9	15.1	125.78	124.92	9
1/27/23	3,400	105½	70	95	160	2,096	.....	.....	...	....	....	0.039	1.32	.....	....	....	.....	.....	.....	9
1/28/23	2,500	105	70	95	160	2,096	1.010	.....	v.ft.	0	+	0.026	0.65	.....	....	7.98	15.1	115.12	114.47	9
Week ending 1/28/23	.....	...	...	...	...	.....	.....	.....	...	....	....	.....	.....	.....	....	8.7	15.1	.....	.....	63
1/29/23	2,650	...	70	95	160	2,096	1.005	.....	v.ft.	0	0	0.039	1.03	.....	....	7.28	15.2	112.57	111.54	9
1/30/23	2,600	...	75	100	170	2,230	1.009	.....	v.ft.	0	0	0.027	0.7	.....	....	7.4	16.9	119.01	118.31	9
1/31/23	2,400	105	70	95	160	2,276	1.007	.....	v.ft.	0	0	0.025	0.6	143 p.m.	....	5.7	15.2	100.80	100.20	9
2/ 1/23	2,400	105	75	100	170	2,241	1.008	.....	v.ft.	0	0	0.022	0.52	.....	....	6.18	16.9	114.55	114.03	9
2/ 2/23	2,600	106	80	110	180	2,510	1.008	.....	0	0	0	0.028	0.73	118 p.m.	....	10.03	17.5	144.60	143.87	9
2/ 3/23	2,550	106	90	110	180	2,510	.....	.....	...	....	.....	0.028	0.71	.....	....	....	17.7	.....	.....	9
2/ 4/23	3,100	106	90	110	180	2,510	.....	.....	...	....	.....	0.037	1.15	.....	....	11.05	17.7	148.33	147.18	9
Week ending 2/ 4/23	.....	...	...	...	...	.....	.....	.....	...	....	....	.....	.....	.....	....	7.9	16.9	.....	.....	63
2/ 5/23	2,500	107	90	110	180	2,510	1.009	.....	v.ft.	0	0	0.036	0.90	.....	....	9.1	17.6	141.21	140.31	9
2/ 6/23	2,600	107	90	110	180	2,510	1.010	.....	v.ft.	0	0	0.037	0.96	.....	....	9.25	17.6	141.76	140.80	9
2/ 7/23	2,600	107	90	110	180	2,510	1.010	.....	v.ft.	0	0	0.045	1.17	.....	....	12.4	17.6	153.26	152.09	9
2/ 8/23	2,500	107	90	110	180	2,510	1.011	.....	v.ft.	0	0	0.042	1.05	.....	....	12.1	17.6	152.16	151.11	9
2/ 9/23	2,600	108	90	110	180	2,510	1.008	.....	v.ft.	0	0	0.056	1.46	.....	....	10.9	17.6	147.78	146.32	9
2/10/23	.....	107	90	110	180	2,510	.....	.....	...	....	....	0.031	0.775	182 p.m.	....	....	.....	.....	.....	9
3/11/23	3,900	107	90	110	180	2,510	1.011	.....	v.ft.	0	0	0.054	2.1	.....	....	....	....	....	.....	9
Week ending 2/11/23	.....	...	...	...	...	.....	.....	.....	...	....	....	.....	.....	.....	....	10.7	17.6	.....	.....	63
2/12/23	2,550	107	90	110	180	2,510	1.010	.....	0	0	0	0.027	6.95	.....	....	12.2	17.6	152.53	145.58	9
2/13/23	2,500	107	90	110	180	2,510	1.011	.....	0	0	0	0.04	1.04	.....	....	11.7	17.6	150.70	149.66	9
2/14/23	2,100	107	90	110	180	2,510	1.008	.....	v.ft.	0	0	0.03	0.63	140 p.m.	....	8.4	17.6	138.66	138.03	12
2/15/23	2,600	107	90	110	180	2,510	1.008	.....	v.ft.	0	0	0.068	1.81	.....	....	9.25	17.6	141.76	139.95	12
2/16/23	2,500	107	90	110	180	2,510	1.008	.....	v.ft.	0	0	0.079	1.97	.....	....	10.5	17.6	146.32	144.35	9
2/17/23	.....	108	110	110	190	2,680	.....	.....	...	....	....	0.08	2	.....	....	....	.....	.....	.....	9
2/18/23	2,300	107	110	110	170	2,267	1.015	.....	v.ft.	0	0	0.83	18.1	.....	....	11.4	17.4	133.61	115.51	..
Week ending 2/18/23	.....	...	...	...	...	.....	....	.....	...	....	....	.....	.....	.....	....	10.6	17.6	.....	.....	60
2/19/23	2,300	107	75	110	120	2,270	1.010	.....	v.ft.	0	0	0.5	11.5	118 Fast.	....	10.8	17.4	131.42	120.92	..
2/20/23	1,700	106	50	100	140	1,864	1.017	.....	v.ft.	+	+	0.45	11	.....	....	11.15	17.4	104.51	93.51	..
2/21/23	1,900	106½	50	100	140	1,870	1.010	.....	v.ft.	0	0	0.071	1.35	.....	....	13.8	16.1	114.37	114.299	..
2/22/23	1,900	107	50	100	140	1,860	1.009	.....	v.ft.	0	+	0.067	1.27	.....	....	8.8	16	96.12	95.85	6
2/23/23	1,800	107	90	110	180	2,420	1.011	.....	v.ft.	0	0	0.067	1.2	.....	....	10.9	17.6	147.78	146.58	9
2/24/23	.....	...	90	110	180	2,420	.....	.....	...	....	....	0.062	1.2	105 Fast.	....	...	17.6	.....	.....	9
2/25/23	2,250	108	90	110	180	2,420	1.010	.....	v.ft.	0	+	0.054	1.2	.....	....	12.4	17.6	153 26	152.06	9
Week ending 2/25/23	.....	...	...	...	...	.....	.....	.....	...	....	....	.....	.....	.....	....	....	....	.....	.....	..
2/26/23	2,300	108	90	110	180	2,420	1.009	.....	v.ft.	0	+	0.05	1.1	.....	....	9 83	17.6	143.87	142.77	9
2/27/23	2,500	108	90	110	180	2,420	1.010	.....	v.ft.	0	+	0.065	1.63	154 p.m.	....	11.1	17.6	148.51	146.88	9
2/28/23	1,900	108	90	110	180	2,420	1.011	.....	v.ft.	0	+	0.058	1.09	.....	....	10.9	17.6	147.78	146.69	9
3/ 1/23	1,900	108	90	110	180	2,420	1.012	.....	0	0	+	0.068	1.25	.....	....	11.1	17.6	148.51	147.26	9
3/ 2/23	2,200	108	90	110	180	2,420	1.012	.....	v.ft.	0	+	0.068	1.5	.....	....	14.2	17.6	159.83	158.33	9

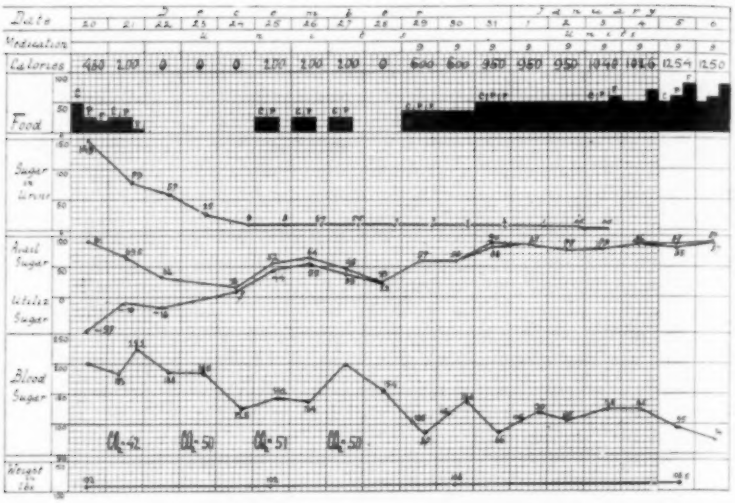

Fig. 1 (Case 1).—Daily graphic of insulin administration, food intake, sugar excretion in urine and amount of glucose utilized; also blood sugar curve, carbon dioxid in blood and the weight of the patient from Dec. 20, 1922, to Jan. 6, 1923; weight December 20, 102 pounds (46.26 kg.).

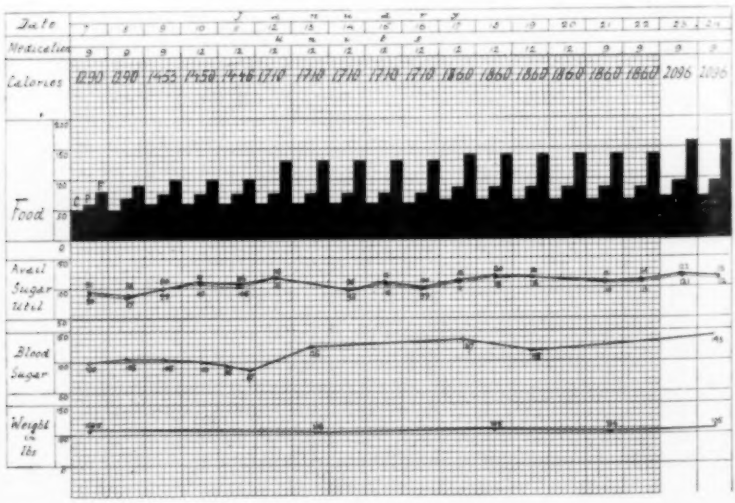

Fig. 2 (Case 1).—Same data as in Chart 1, for period January 7 to 24.

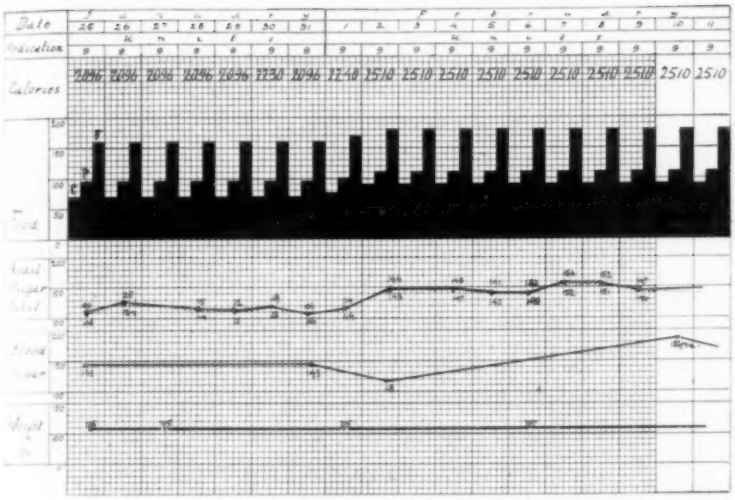

Fig. 3 (Case 1).—Period from January 25 to February 11.

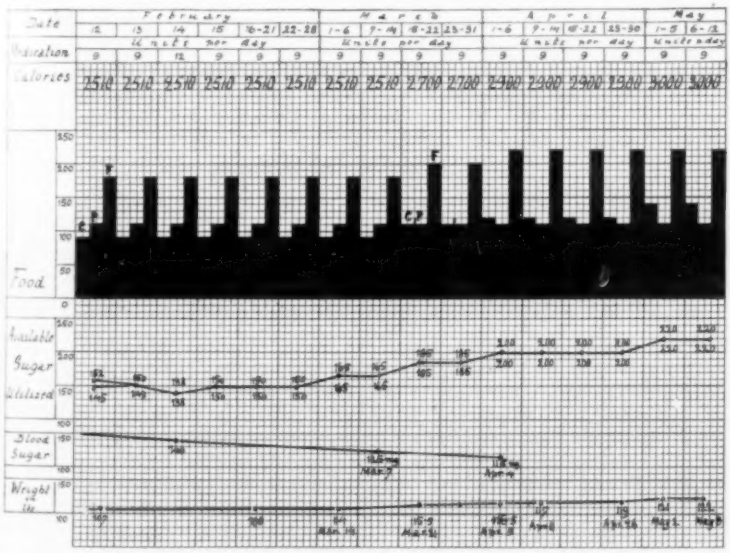

Fig. 4 (Case 1).—Period from February 12 to May 12; weight, May 12, 122 pounds (55.33 kg.).

losing weight rapidly. A diagnosis of diabetes was made. The patient had had measles, scarlet fever and pneumonia in childhood. His family history was negative.

Physical Examination.—This revealed nothing of importance, except two bad teeth, which were removed. On admission to the hospital he weighed 98 pounds (42.45 kg.); on May 1, 1923, 112 pounds (50.8 kg.). Sugar in the urine was 20 gm.; blood sugar, 300 mg.

Treatment and Course.—As the patient was much emaciated, he was put on insulin immediately, and the diet was rapidly increased to a maintenance value of 2,000 calories; the insulin dosage was increased simultaneously from 15 to 45 units. The patient was an unintelligent person who constantly stole food in spite of gain in weight and a sufficient diet, so that we regard the outcome of his case when discharged from the hospital as problematical. Tooth infection was present in this case also.

CASE 3.—*History.*—A man, aged 31, married, a clerk, born in Russia, had had diabetes for one year. He was admitted to the hospital on Jan. 8, 1923, and discharged on March 22, 1923. The patient had the usual symptoms of diabetes. He had had an appendectomy performed in 1921. There were no other infections. The family history could not be obtained. His parents were in Russia.

Physical Examination.—The examination was negative. The patient's weight on admission was 94 pounds (40.63 kg.); weight on discharge, 101½ pounds (46.03 kg.). The sugar content of the urine was 70 gm.; the blood sugar, 65 mg.

Treatment and Course.—The patient was put on a low diet, and on account of acidosis fat was excluded. He was starved on the sixth and seventh days, becoming practically sugar free. Twelve units of insulin were given on the ninth day on a diet of carbohydrate, 25 gm.; protein, 50 gm.; fat, 50 gm. On 12, and later 9 units of insulin, the diet was increased to 1,560 calories, and finally to 2,250 calories, with an insulin dosage of 18 units, rendering him not quite sugar free. The case was complicated by a tendency to steal. The weight increased gradually. As he was a person of low intelligence, an effort was made after two months of treatment to put him on a diet of 1,300 calories without insulin. Sugar, however, reappeared on this diet, and on his own insistence he was sent home on insulin, but he has not reported to the follow-up clinic. His case is of importance as illustrating the difficulty of treating a diabetic patient who will not cooperate, and whose grade of intelligence is low.

CASE 4.—*History.*—A man, aged 47, married, a policeman, born in Ireland, had had diabetes since September, 1922. He was admitted to the hospital on Nov. 20, 1922; he was discharged on Jan. 26, 1923. He had had no infectious diseases. He took whisky every day. His family history was negative.

Physical Examination.—This revealed nothing of importance but an enlarged liver.

Treatment and Course.—He was given insulin from Dec. 18, 1922, to Jan. 18, 1923, receiving 9 units the first two days, 12 units the next twelve days, 15 units for the next six days and 18 units for the remaining 9 days. His weight on admission was 170 pounds (77.11 kg.); weight on discharge, 166 pounds (75.29 kg.). He was sugar free on 1,520 calories and 50 gm. of carbohydrate. While on insulin, the patient was receiving a diet consisting of 70 gm. of carbohydrate, 100 gm. of protein and 190 gm. of fat. On January 18, insulin was stopped, and the diet changed to 50 gm. of carboydrate, 60 gm. of protein and 140 gm. of fat, on which he remained sugar free. He is being followed in the diabetic clinic and is sugar free at the present time on more or less the same diet.

Comment.—The patient in the foregoing case is of interest because he shows slight increase in pancreatic function after a month's treatment

with rather small doses of insulin. On a diet of 1,610 calories he was able to utilize 92 gm. of glucose; on the same diet in the after period he utilized 104 gm., a gain of 12 gm. a day. Sugar utilization during the preliminary period was 91 gm.; last week observed, 123 gm.; after period, 104 gm.; per insulin unit, 1.7 gm.

Case 5.—*History.*—A woman, aged 33, married, a clerk, born in the United States, had had diabetes for six years. From 1911 until 1918 she was subject to frequent attacks of quinsy sore throat. She remembered having quinsy on Thanksgiving day, 1917, and again in February, 1918. In March, she was said to have had diabetic coma. She was told by a physician, in 1917, that she had diabetes. In June, 1918, her tonsils were removed; since then she had felt much better. She had had measles, scarlet fever and whooping cough when a child. She had been married for fifteen years. She had two children, aged 9 and 12, respectively. She had had a therapeutic abortion because of diabetes in May, 1918; no miscarriages. Her father died of diabetes at the age of 45. Otherwise the family history was negative.

First Admission.—She was admitted on Aug. 2, 1922, and discharged on Aug. 19, 1922. She showed 3 per cent. of sugar in the urine and 200 mg. of blood sugar and a faint trace of diacetic acid and acetone. Her weight on admission was 120 pounds; weight Aug. 12, 1922, 117½ pounds (53.29 kg.). The patient became sugar free in three days on a diet consisting of 50 gm. of protein, 50 gm. of carbohydrate, and 50 gm. of fat, with one starvation day. She was discharged on August 18, receiving 100 gm. of carbohydrate, 100 gm. of protein and 120 gm. of fat, showing a faint trace of sugar in the urine. In the diabetes clinic, where she was under observation up to her second admission, examination revealed sugar at intervals.

Second Admission.—The patient was readmitted on Dec. 11, 1922, and put on insulin medication on Dec. 19, 1922.

Physical Examination.—The examination was negative. The patient's weight on Dec. 15, 1922, was 115½ pounds (52.38 kg.); her weight on May 1, 1923, was 124 pounds (56.24 kg.).

Treatment and Course.—On her readmission she was rendered sugar free by undernutrition. The diet was not a maintenance one, showing a tolerance of 66 gm. of sugar on a diet of 1,000 calories. The blood sugar, however, varied from 170 to 214, a high threshold. The patient was, therefore, put on a small dosage of insulin, 3 units a day, which was increased with the increase in her diet to 12 units when on the twenty-fourth day she showed slight symptoms of insulin shock with a blood sugar content of 76 on a diet of 1,350 calories. The symptoms consisted of nervousness, tremor and sweating, which disappeared rapidly after the administration of a glass of orange juice. During the subsequent two days she was kept on a 9 unit dosage, the blood sugar rising to 182 mg. in the morning and 166 mg. in the afternoon, when she was again given 12 units of insulin without having any symptoms. As she continued to lose weight on this diet, the number of calories in her diet was increased, first to 1,860, then to 2,295 on February 3, with an insulin dosage of 18 and finally 29 units. The course of her disease has been interrupted by several diarrheal attacks, and at present she is on a diet containing 120 gm. of available glucose. Her carbohydrate utilization per insulin unit has varied with different lots of insulin—3.5, 2.4, 1.6, 3.5, 3.2, 3.2, 2.9 and 3 gm.

Comment.—The patient had a moderately severe diabetes, but could not maintain herself sugar free on a maintenance diet. On a somewhat large dosage of insulin she is now maintaining herself, and instead of

being in her previous condition of emaciation is approximately of normal weight. She is able to do her work without fatigue, and has thus regained her economic status.

CASE 6.—*History.*—A woman, aged 50, a widow, a housewife, born in Austria, had had diabetes for seven years. She was admitted to the hospital Jan. 2, 1923, and discharged on March 8, 1923. She complained of inability to walk because of severe pain in her left knee. She had had measles, diphtheria, whooping cough and frequent attacks of cold and sore throat, especially during the last seven years. She had been married for twenty-five years. She had never been pregnant. Menopause occurred at the age of 47. Her father had died of diabetes at the age of 60. Her mother was living and well. Two sisters and one brother were well. One sister had diabetes. Her husband died of blood poisoning.

Physical Examination.—The patient had large, infected tonsils (operation refused) and evidences of osteo-arthritis in both knees. There was also a low grade infection of the sinuses. Her weight on admission was 125 pounds (56.69 kg.); on discharge it was 129 pounds (58.31 kg.). Sugar content of the urine was 50 mg.; blood sugar, 250 mg.

Treatment and Course.—In the hospital she was kept on a low diet for ten days with one day of actual starvation, with the result that at the end of that time on a diet of 260 calories with 43 gm. of available sugar she was excreting 12 gm. of sugar in the urine with a blood sugar content of 232 mg. She was then given insulin—at first 9 units and later 12 units; the diet was gradually increased to 2,000 units with 138 gm. of available sugar; she was then sugar free with a blood sugar of 130 mg.

Comment.—This patient also presents the clinical picture of a severe diabetes, manufacturing sugar from her body protein on a low diet. Her condition was easily controlled by small doses of insulin. The sugar utilization of her preliminary period was 32 gm.; during February, 5 gm. of carbohydrate utilization per insulin unit, and on discharge 7.7 gm. per insulin unit, showing in all probability an increase in pancreatic function.

CASE 7.—*History.*—A school girl, aged 8, born in the United States, was admitted to the hospital on Jan. 25, 1923, and discharged on April 18, 1923. Three months prior to admission the three youngest of the six children in the family became jaundiced. (In the same school there were also fourteen other cases of jaundice). The jaundice lasted for about one month, when the three children developed a ravenous appetite and drank large quantities of water. All three began to lose weight rapidly, in spite of the fact that they were consuming large amounts of food. Two weeks after the jaundice cleared up the three children came down with scarlet fever. Examination of the urine made at that time revealed 2 per cent. of sugar for the other two children, while Rose had 5 per cent. with a polydipsia and polyphagia. Apparently this dated from the onset of the jaundice. This child had had measles at the age of 3 weeks, chickenpox and whooping cough at the age of 3, German measles when 4 years old and mumps at the age of 6. All three children were admitted to St. Luke's Hospital. The other two had a mild form of diabetes, and are now sugar-free on a moderately restricted diet.

Physical Examination.—Physical examination of Rose was negative. Her weight on admission was 35 pounds (15.87 kg.); on discharge it was 42¾ pounds (19.39 kg.). The sugar content of the urine was 42 mg.; the blood sugar, 82 mg. Sugar utilization during the preliminary period was 64 gm. Sugar utiliza-

tion during last week observed was 133 gm. Sugar utilization per insulin unit was 8 gm. On admission she was passing 42 gm. of sugar on a diet giving her 51 gm. of available sugar. The blood sugar was 182 mg.; carbon dioxid content, 44.

Treatment and Course.—On the third day she was given 4 units of insulin to control acidosis, and on the thirtieth day her blood sugar was 120 mg.; the carbon dioxid content was 52 mg. The diet was rapidly increased to a maintenance diet of 2,020 calories containing 145 gm. of available sugar. At this time she was receiving 8 units of insulin a day. Her total gain in weight was 10 pounds (4.5 kg.), and instead of being an emaciated, unhappy child she is now a normal little girl. At the time of discharge she had a little sugar in the urine, probably due to stealing—a trick she had learned from two little boys in the ward.

Comment.—The interesting fact about the family in Case 7 is the development in three of its members of diabetes following infectious jaundice, of whom a girl aged 8 had the only severe case. The blood sugar curves after glucose ingestion of the other two, however, were typically diabetic, although they were readily kept sugar free by moderate restriction of diet, simply eliminating sugar and sweets. We wish to emphasize the fact of the importance of acute infections in relationship to the onset of diabetes.

Case 8.—*History.*—A school boy, aged 7, born in the United States, had had diabetes for three years. He had had two previous admissions, and was discharged, sugar free, on a fairly good tolerance of carbohydrate, 60 gm.; fat, 60 gm., and protein, 90 gm.; but at home he would not live on his diet, and he was readmitted on Sept. 9, 1922. After an unsuccessful effort to render him sugar free by undernutrition, he was put on a diet of approximately 1,000 calories, showing sugar continuously, and with a blood sugar of 182 mg. He had been reduced to a skeleton, weighing 40 pounds (18.14 kg.). His father was living and well; his mother died of pneumonia; his aunt had diabetes.

Physical Examination.—The examination was negative except for extreme undernutrition.

Treatment and Course.—When insulin became available, he was kept on a 1,000 calory diet, and on this showed glucose utilization of 61 gm., although he was passing at the time from 40 to 60 gm. of sugar in his urine. He had been an inveterate stealer of food, and for that reason was kept for the first six weeks of the insulin experiment in a room by himself under lock and key. On an insulin administration of 9 units he was rendered sugar free, on a diet containing 1,500 calories and 123 gm. of available sugar, his blood sugar falling from 182 to 125 mg., and at times in the afternoon as low as 55 mg. without symptoms of hypoglycemia. The diet was gradually increased, until at the end of April he was receiving 2,100 calories on 27 units of insulin a day, showing, however, at times 5 gm. of sugar. His weight, which had been low, continued so until nitrogen equilibrium was established, at which time he was getting a diet of approximately 1,600 calories, from which time on it rapidly increased until on his discharge he weighed 64½ pounds (29.25 kg.). His stealing propensity, however, made the case difficult. On one occasion he even forged his diet orders. It is, therefore, not surprising to find that at the mid-period, when not perfectly controlled, his utilization per insulin unit varied. He took care at one time of 7 gm. of glucose per unit: in the period from February 13 to February 20, 3 gm., and in the period from April 25 to 30, 4 gm. per unit. He is now at home on insulin treatment, perfectly trained in the simple analysis of his urine and in the calculation of his diet.

Comment.—Treatment of this patient will probably not be successful, as in spite of an overliberal diet on which it seemed wise to put him he will probably take additional food. Although he had severe diabetes and his pancreatic function had been much impaired by dietary excess, he was perfectly amenable to treatment. Incidentally, this is the

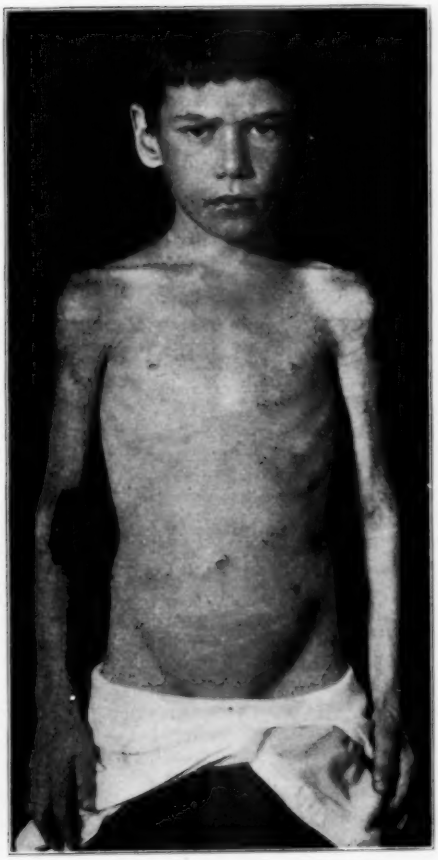

Figure 5

Figure 6

Figure 7

Fig. 5 (Case 8).—Taken Dec. 20, 1922, before administration of insulin. Weight, 40 pounds (18.1 kg.). Note extreme undernutrition and facial expression.

Fig. 6 (Case 8).—Jan. 29, 1923; weight, 48½ pounds (21.9 kg.).

Fig. 7 (Case 8).—March 10, 1923, weight, 55 pounds (24.9 kg.). Weight May 1, 1923, was 64½ pounds (29.2 kg.).

one patient in our series who showed an anaphylactic reaction consisting of marked urticaria. In this case one of the earlier preparations of insulin was used. The condition was rapidly controlled by desensitization with fractional doses, after which insulin was again administered.

Case 9.—*History.*—A woman, aged 53, single, a housewife, born in France, had had diabetes since 1913. She was admitted on March 3, 1923, in coma, with signs of lobar pneumonia. She was discharged on April 25, 1923. She had been subject to attacks of asthma since she was 20 years old. Her last attack occurred in 1920. Since then she had been free from attacks. She had diphtheria when she was 20 years old. Her tonsils had been removed at the age of 21. She had had a carbuncle in 1922. Her mother's aunt had diabetes.

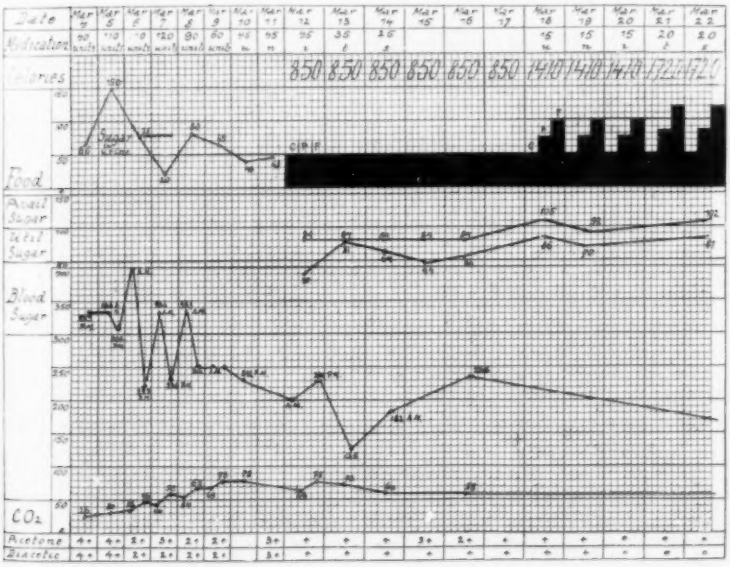

Fig. 8 (Case 9).—Patient in coma on admission, showing 66 gm. of sugar in urine, 333 mg. in blood, carbon dioxid 26 per cent. by volume, acetone and diacetic acid 4+ with physical signs of lobar pneumonia. At the end of ten days, during which she received 700 units of insulin as shown above, she was able to utilize 80 gm. of glucose, the blood sugar fell to 125 mg; the carbon dioxid rose to 72 per cent. by volume; acetone and diacetic acid were 1+. On March 20, the patient was free from acidosis.

Her grandfather had died in an attack of asthma. On March 26, 1923, she weighed 117 pounds (53.07 kg.); on May 12, 1923, 126 pounds (57.15 kg.).

Physical Examination.—Examination revealed pneumonia of the right middle and lower lobes. Sugar utilization during the preliminary period was 35 gm.; sugar utilization during last week observed, 105 gm.; sugar utilization per insulin unit, 1.4 gm.

Treatment and Course.—She was admitted to the hospital in coma with a Group IV pneumonia, a blood sugar content of 333 mg., and a carbon dioxid

content of 26. Forty units of insulin were given at once. On a dosage of 110 units of insulin daily the acidosis was controlled within forty-eight hours, the pneumonia running its usual course with defervescence on the eighth day. During the acute illness the diet at first consisted of gruel and orange juice; later milk was added, and on March 12, the patient was put on a solid diet of carbohydrate, 50 gm.; protein, 50 gm.; fat, 50 gm.; this was subsequently increased to 2,200 calories with 165 gm. of available sugar. May 12, she had been sugar free for a month, with a blood sugar of 111.

Comment.—The case is one of those almost invariably fatal when treated by the old method—a coma complicating a severe acute infection—and shows that with insulin the coma may be relieved when the infection runs its ordinary course.

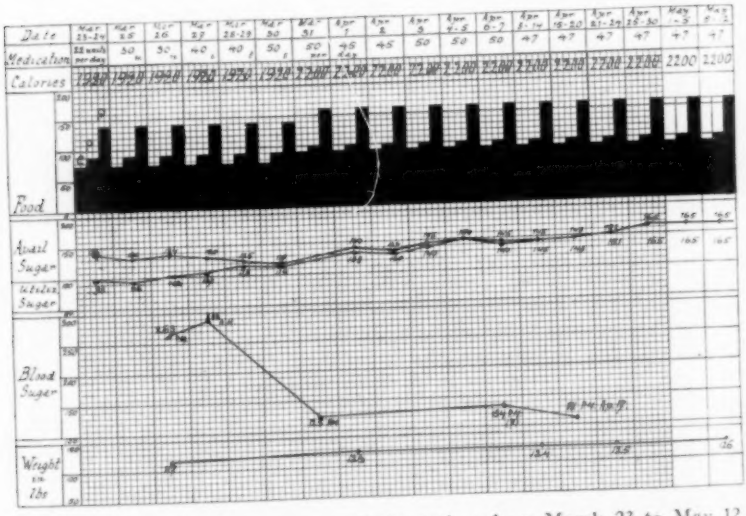

Fig. 9 (Case 9).—The progress of the patient from March 23 to May 12, giving daily dose of insulin and the diet, showing also the amount of glucose utilized, the blood sugar curve and the weight.

Case 10.—*History.*—A school boy, aged 8, born in the United States, had had diabetes for one year. He was admitted to the hospital on April 13, 1921, and discharged on June 30, 1922. A month prior to admission he had had an attack of German measles which had lasted several days. After recovery his mother noticed excessive thirst, hunger and polyuria, with gradual loss of weight and drowsiness. He was taken to a physician, who made a diagnosis of diabetes. The family history was negative. Past history was negative, except for German measles.

Treatment.—The patient was discharged from the hospital sugar-free on a diet consisting of 120 gm. of fat, 70 gm. of protein and 150 gm. of carbohydrate. He was followed up in the pediatric clinic and on December 22, the Klebs-Löffler bacillus was found in his throat. He was sent to a municipal hospital, where his diet was neglected. The diabetes became much worse, and acetone appeared in the urine again in January, 1923. He was readmitted to the hospital

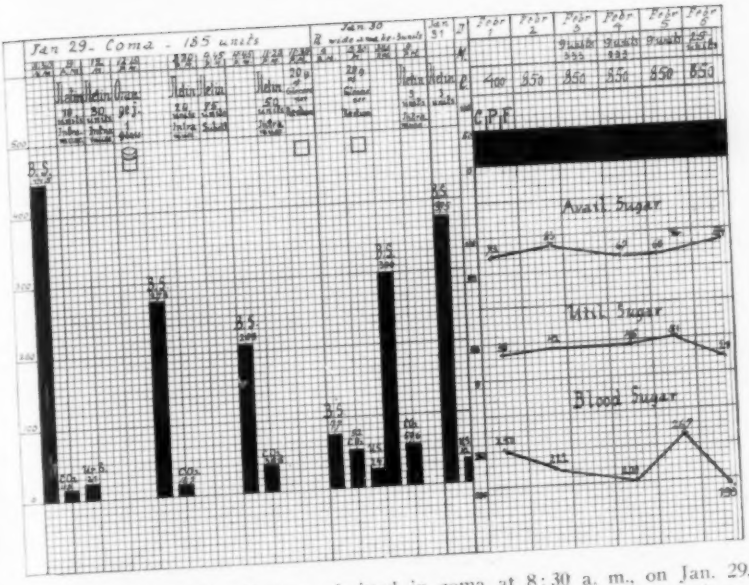

Fig. 10 (Case 10).—Patient admitted in coma at 8:30 a. m., on Jan. 29, 1923. Observe rapid fall of blood sugar from 445 mg. to 77 mg. and rise of carbon dioxid from 11.8 to 52 per cent. by volume following administration of 185 units within twenty-four hours when he came out of the coma.

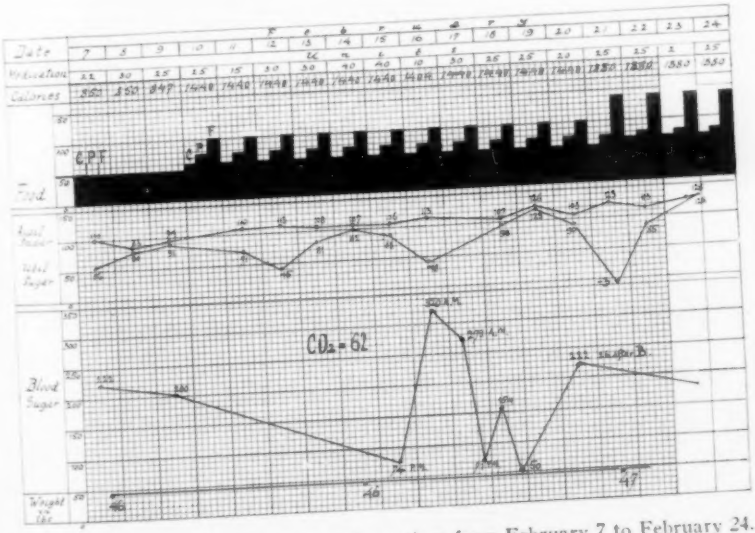

Fig. 11 (Case 10).—Progress of the patient from February 7 to February 24. Note marked increase in diet.

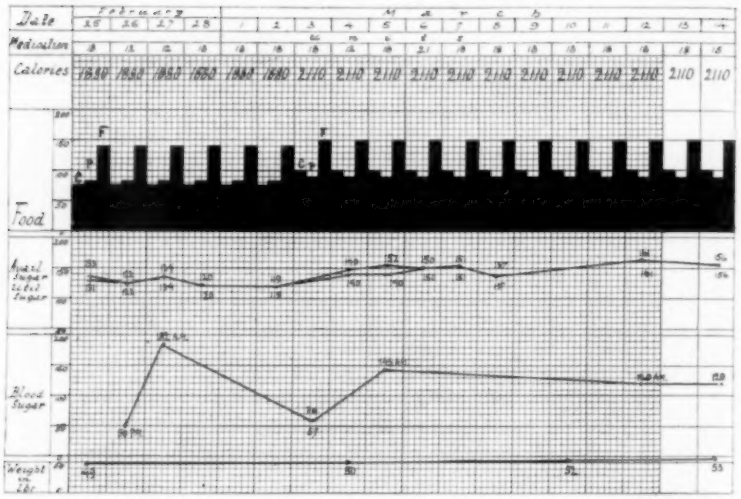

Fig. 12 (Case 10).—Period from February 25 to March 14.

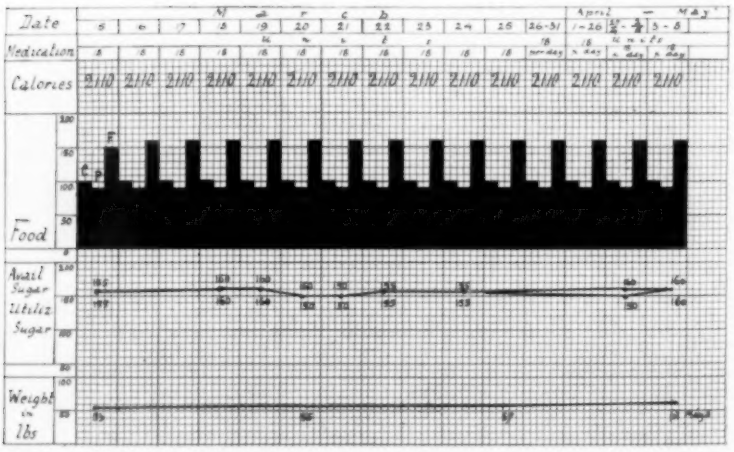

Fig. 13 (Case 10).—Period from March 15 to May 8. The patient was now utilizing 155 gm. of glucose; daily dose of insulin, 18 units; increase in weight since February 7, 15 pounds (6.8 kg.).

for the second time in coma. His weight on admission was 46 pounds (20.86 kg.); the carbon dioxid content of the blood was 11.8. His weight on discharge, May 8, 1923, was 61 pounds (27.66 kg.); the carbon dioxid content of the blood was normal. He was then put on a diet consisting of 90 gm. of protein, 150 gm. of fat and 120 gm. of carbohydrate. The sugar utilization during the preliminary period was 40 gm.; sugar utilization per insulin unit during February was 5.2 gm.; during April, 6.6 gm.

Treatment and Course.—The patient was admitted on January 29, in coma, with a blood sugar content of 445 mg. and a carbon dioxid content of 11.8 per cent. by volume. He was given 10 units of insulin before the results of the examination of the blood were learned. Then 30 units more were given; at noon the blood sugar had fallen to 273 mg. and the carbon dioxid content had risen to 13.7. At 3 p. m., 20 units of insulin were given, and an hour later as he was still in coma 75 units were given. As the blood sugar had fallen to 208 mg. and the carbon dioxid content had risen to 38.5 at 11 p. m., 50 more units were given with 20 gm., of glucose. The total dose for the day was therefore 185 units. The following forenoon the boy was awake but restless and sweating. The blood sugar content was 77 mg. and the carbon dioxid 52. Twenty gm. of glucose were given, the blood sugar content rising by afternoon to 300 mg., and carbon dioxid to 57.6, when 3 units of insulin were given. The patient was fed during the day on oatmeal gruel. An interesting complication, the only one observed in our series, was a hematuria, which we attributed to the cresol used in preserving the drug at that time, insulin-Lilly, H-5, containing 5 units per cubic centimeter, thus necessitating the injection of large amounts of fluid—37 c.c. in one day. As he was able to utilize in a preliminary period 40 gm. of sugar, a daily dosage of 9 units increased to 30 in a few days rendered him sugar free by February 8, and he was finally stabilized on a diet of 2,110 calories with 160 gm. of available carbohydrate on 18 units of insulin daily. (See charts.)

Comment.—The foregoing case is interesting as illustrating a coma due to dietary excess in a child who previously had had good tolerance. Large doses of insulin were required to reduce the acid poisoning, and it is to be noted that even with the administration of glucose and orange juice a mild carbohydrate shock was produced at a blood sugar level of 77 mg., relieved by glucose solution. It is also of interest to note that in this case a blood sugar of 50 mg. was unattended by symptoms. In this case also an infectious disease—German measles—is said to have preceded the onset of diabetic symptoms.

Case 11.—*History.*—A woman, aged 55, single, a seamstress, born in the United States, was admitted to the hospital in a coma on Jan. 2, 1923. She died on Jan. 3, 1923. No history was obtainable.

Physical Examination.—The patient had a well developed bronchopneumonia. Laboratory findings: There were 533 mg. of blood sugar per 100 c.c.; the carbon dioxid tension was 10. Three hours before death the blood sugar content was 230 mg. and the carbon dioxid tension 25.

Treatment and Course.—The patient was admitted in a coma at 8:30 p. m., dangerously ill with bronchopneumonia. Fifty units of insulin were at once administered, with 20 gm. of glucose; the blood sugar was 533 mg.; carbon dioxid, 10. As there was no improvement, 50 units were again given at midnight, and this dosage was increased by another 50 units at 4 a. m.; at this time blood

sugar content was 440 mg. Fifty units were again given at 9 a. m. and 75 at 3 p. m., with a drop in the blood sugar to 230 mg. and a rise in carbon dioxid to 25. The total insulin dosage was 275.

Necropsy.—Necropsy revealed bronchopneumonia of the right middle and lower lobes, arteriosclerosis and fibromyoma uteri.

Comment.—This case is of value as illustrating an excellent chemical result—a drop in blood sugar from 533 to 230, a rise in carbon dioxid tension from 10 to 25, with a great diminution of the ketonuria. Death, however, resulted from the pneumonia, which of course was in no way influenced by the insulin treatment.

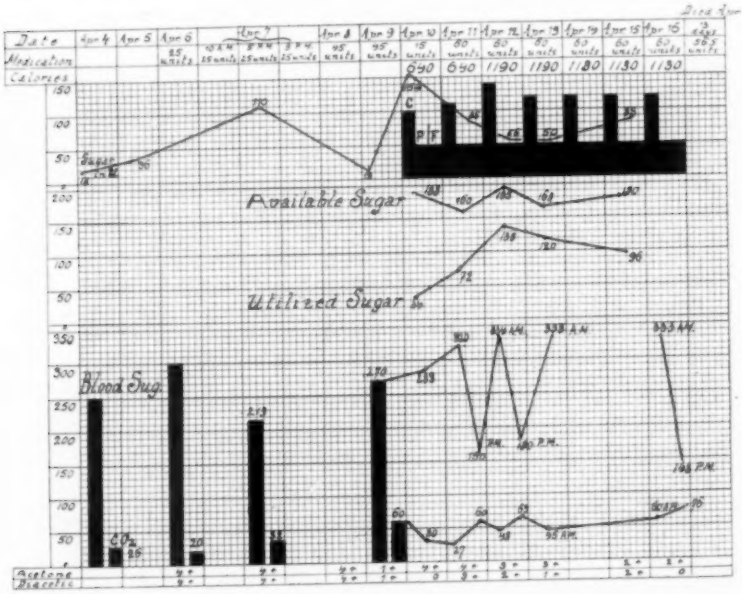

Fig. 14.—Data in Case 12.

Case 12.—*History.*—A man, aged 54, a letter carrier, born in Ireland, had had diabetes for five years. He was admitted to the hospital on May 1, 1922. He was discharged on June 17, 1922, on a diet containing 84 gm. of protein, 84 gm. of fat and 76 gm. of carbohydrate. The patient was followed in the diabetic clinic. He was readmitted to the hospital on April 2, 1923, with a carbuncle of the neck which had started five days prior to admission. His past history was negative, except for bad teeth. His family history was negative.

Physical Examination.—On the second admission he had a large carbuncle at the back of his neck, and a temperature of 103 F. A blood culture contained *Staphylococcus albus.*

Treatment and Course.—The patient was admitted with a carbon tension of 26, which rose to 60 on April 9, and remained normal until he died. When first seen by the medical division he was given insulin, at first 25 units daily and then 45 and 60 units. While acidosis was rapidly relieved on this treatment

on a diet of 100 gm. of carbohydrate, 50 gm. of protein and later 50 gm. of fat, he succumbed later to a blood sepsis. He was operated on April 4—a simple crucial incision and packing. He died on April 19, 1923.

Necropsy.—Necropsy revealed bronchopneumonia with multiple abscesses throughout the entire lung. The heart showed fibrinous pericarditis. The spleen was large, soft and of the septic type. Both kidneys contained a number of small abscesses.

Comment.—This case admirably illustrates chemical improvement without effect on the underlying infection.

CASE 13.—*History.*—A man, aged 56, married, a tradesman, born in Germany, had had diabetes since 1910. He was admitted to the hospital on Nov. 10, 1922. In January, 1921, his left toe became sore and later black. His left foot was amputated at the lower third of the tibia, in September, 1921. The right toe became sore in May, 1922, and black in December, 1922. He had had no infectious diseases. His teeth started to decay rapidly about 1910, when diabetes started.

Physical Examination.—Examination revealed an enlarged liver, a gangrenous toe and marked arteriosclerosis. His left leg had been amputated at the lower third of the tibia.

Treatment and Course.—He was put on insulin treatment on Jan. 4, 1923, to Jan. 18, 1923, when it was stopped because of the low supply. Insulin treatment was started again on March 5, and continued until March 31. His weight on January 4, was 110 pounds (49.89 kg.) and it is now 117 (53.07 kg.). The gangrenous toe of his right foot is about ready to fall off.

Comment.—This case of diabetes was of long standing, but on a maintenance diet of 1,760 calories the patient was maintained sugar free. He was put on insulin treatment with the idea of performing a surgical operation. His reaction to insulin, however, was less marked than in any case in our series, 1 unit enabling the utilization of only 0.9 gm. of glucose. As it was decided that it was better to permit his gangrenous toe to slough off than to amputate above the knee, he was put back on his maintenance diet, and is still in the hospital.

COMMENT

In our series there have been six cases of diabetic coma, only one uncomplicated by an infection. Infections whose course lasted for twenty-four hours were all influenced chemically by insulin treatment, but the patients succumbed to the infection, with the exception of the patient with pneumonia reported above (Case 9), who made a perfect recovery, and is now sugar free. The patient with the uncomplicated case recovered, making a percentage of recovery in the series of 33⅓.

Of the series, there is a history of diabetes immediately after an acute infection in six cases. The cases of the three children in Case 7 are particularly striking, and followed an infectious jaundice. Case 10 followed measles and Case 1 a tooth infection. It has long been recognized that an acute infection causes a rapid exacerbation of diabetic symptoms, but we feel that the possibility of diabetes resulting from the

loss of the pancreatic function secondary to an infection has been neglected, and urge the collection of data on this point. Epithelial gland infections following the ordinary infectious diseases of childhood are common enough phenomena, as for instance orchitis in mumps.

SUMMARY

1. Insulin treatment will invariably raise the carbohydrate tolerance both in mild and in severe diabetes.

2. Acidosis even in its severe form of coma can often and perhaps usually be controlled, if uncomplicated by infection.

3. In certain instances the pancreatic function seems not only to be spared, but also to be increased by insulin treatment.

4. Hypoglycemia, while a real danger, can readily be guarded against and overcome by balancing the diet against insulin administration.

5. Diet must be more carefully maintained than in the case untreated by insulin.

6. Education of the patient, both in the calculation of his diet and the simple analysis of his urine, and in the symptoms of hypoglycemia, must be insisted on. This procedure is by no means as difficult as it appears, and any ordinarily intelligent person can be sufficiently instructed.

CLINICAL STUDIES OF DIGITALIS

I. EFFECTS PRODUCED BY THE ADMINISTRATION OF MASSIVE DOSAGE TO PATIENTS WITH NORMAL MECHANISM *

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It has long been known that the administration of digitalis to patients with heart disease produces striking clinical improvement in many cases. Students of cardiology have long been occupied with two closely related problems: (*a*) a differentiation of those cases that are improved, from those that are not benefited by the drug; (*b*) an explanation of its action, and an understanding of the manner in which it produces improvement. Little progress was made toward a solution of these problems until recent years, and even now, although advancement has been rapid, no more than a fair beginning has been made.

A few facts have been established. It is well known that digitalis causes considerable delay in auriculoventricular conduction in many patients, and careful studies [1] have indicated that prolongation of a-v conduction of greater or less degree is a constant effect of the drug in all cases. The exact mechanism by which this depression of conduction is brought about, or rather the degree to which the contributing factors are responsible, is not yet completely understood in all its details. That it is, however, responsible for the ventricular slowing which is produced by the administration of digitalis to patients with auricular fibrillation and rapid ventricular rate, there seems to be little reason to doubt. That this ventricular slowing by prolonging diastole, both relatively and absolutely, results in increased cardiac efficiency, can hardly be questioned; for slowing parallels improvement in symptoms, and on withdrawal of the drug, increased ventricular rate is attended by a recurrence of the symptoms of impaired circulation. There is, then, general agreement that digitalis causes improvement in patients with auricular fibrillation by producing ventricular slowing through a depression of a-v conduction, thus allowing the ventricle more rest. But is this the sole factor in the improvement in such cases? Is there any other action of the drug that exerts a favorable influence in cases of auricular fibrillation, in addition to its action on the conducting tissues by virtue of which it produces slowing of the ventricle?

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* Read before the Saint Louis Medical Society, May 22, 1923.

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1. Cohn, A. E.: Clinical and Electrocardiographic Studies on the Action of Digitalis, J. A. M. A. **65**:1527 (Oct. 30) 1915.

Robinson,[2] in estimating the rapidity and persistence of the action of digitalis on hearts showing auricular fibrillation, based his conclusions entirely on the occurrence of ventricular slowing and made this the sole criterion in his determinations. No other evidence of any beneficial action can be so readily demonstrated on patients. No other criterion of effect can be so easily applied as a determination of changes in rate. Lewis [3] finds no evidence of any "other important action of the drug on the human heart" and attributes the beneficial effect of digitalis in such cases solely to the slowing of the ventricle through depression of a-v conduction.

This view takes no account of any favorable action of the drug directly on the ventricular muscle, and *limits the therapeutic use of digitalis, generally speaking, to cases that exhibit fibrillation of the auricles.* MacKenzie [4] holds practically the same opinion, although he thinks that in cases of heart failure which are not associated with auricular fibrillation, digitalis should be tried, since "we are forced to try all sorts of remedies" and "drugs of the digitalis group offer the best prospects."

Directly opposed to this view is the opinion held by most clinicians and by certain eminent investigators. Eggleston,[5] Pratt,[6] Christian,[7] and West and Pratt [8] have all noted evidences of favorable action from the administration of digitalis to patients with normal rhythm.

In view of such diversity of opinion, then, the question of the beneficial effect of digitalis in patients with normal cardiac mechanism seemed to demand further study. Particularly was this true since the problem is attended by difficulties greater than are encountered in a study of its action in auricular fibrillation, and since an accurate estimation of its effects in patients with normal mechanism is more difficult to reach. It is evident that no benefit in cases with normal mechanism can be expected to result generally speaking from that action of digitalis to which is usually ascribed its beneficial result in fibrillation of the auricles. No depression of a-v conduction will produce ventricular slowing in cases with normal mechanism (unless heart block be induced); and any effect on the musculature that might increase the

2. Robinson, G. C.: The Rapidity and Persistence of the Action of Digitalis on Hearts Showing Auricular Fibrillation, Am. J. M. Sc. **159**:121 (Jan.) 1920.

3. Lewis, Sir Thomas: On Cardinal Principles in Cardiological Practice, Brit. M. J. **2**:621 (Nov. 15) 1919.

4. MacKenzie, Sir James: Principles of Diagnosis and Treatment in Heart Affections, Oxford Medical Publication, 1918.

5. Eggleston, Cary: Digitalis Dosage, Arch. Int. Med. **16**:1 (July) 1915.

6. Pratt, Joseph H.: Digitalis Therapy, J. A. M. A. **71**:618 (Aug. 24) 1918.

7. Christian, H. A.: Digitalis Therapy, Satisfactory Effects in Cardiac Cases with Regular Pulse Rate, Am. J. M. Sc. **157**:593 (May) 1919.

8. West, H. F., and Pratt, Joseph H.: Clinical Experience with a Standardized Dried Aqueous Extract of Digitalis, J. A. M. A. **75**:77 (July 10) 1920.

efficiency of the ventricle is difficult to measure. Dependence must be placed on any indirect evidence of benefit that may be shown in these cases. The effect of any coincident factor whose influence is known to be favorable, such as rest in bed, must be eliminated.

The value of most of the clinical studies that have been made of the problem has seemed to be impaired by the failure of the investigators to supply sufficient quantitative estimations of the beneficial effects of rest. In order to justify the conclusion that any improvement that follows the administration of digitalis is due to the action of the drug, there must be a clear idea of the patient's *rate of progress* before the drug was given; and it must be shown that this rate of improvement was accelerated after the administration of the drug. Quantitative data must be supplied rather than the impressions obtained by the investigator. A statement of the output of urine or of the exact heart rate before the patient was given digitalis, and similar data for the period following, carry more conviction than the mere statement that diuresis or that slowing did or did not occur.

It appeared that data of this sort were inadequate in most of the studies referred to above that indicate a beneficial action of the drug, particularly in view of the opposite opinion held by so eminent a student as Sir Thomas Lewis. In administering digitalis to patients with regular heart action, little evidence of improvement had ever come under my observation which could not reasonably be explained without the assumption that it was due to the action of the drug. This fact and the weight of opinion expressed by Lewis and MacKenzie inclined me to believe that digitalis is of no value in patients with normal mechanism. It was determined, however, to attack the problem with as little as possible of preconceived opinion.

The main object has been to determine: (*a*) whether there is any evidence that digitalis has a favorable action on patients with heart disease other than those with auricular fibrillation (or flutter). If evidence of such an effect should be exhibited, further problems would be: (*b*) to note exactly just what are the results of such action; (*c*) to determine, if possible, what classes of patients with normal rhythm are so affected by the drug; and finally, (*d*) to seek an explanation of the mechanism by virtue of which such effects are produced.

METHOD OF STUDY

The present study was conducted as follows: Patients with normal cardiac mechanism who showed evidence of decompensation or symptoms that might be accounted for either in whole or in part on that basis, were put to bed and given a restricted diet, a measured amount of fluid, and no drug that might affect the heart or kidneys. This was continued for a period of one, two or more weeks. At the beginning of this period

of observation the condition of the patient was determined as accurately as possible, and the findings noted in his record. Particular care was taken to note the heart findings, evidence of congestion of the lungs, hydrothorax, size of the liver, amount of edema, body weight, amount of urine, electrocardiogram, vital capacity, blood pressure, nonprotein blood nitrogen, urine findings and the patient's symptoms. A Wassermann test was made on the blood of all patients. None had continuous fever.

During this preliminary period frequent observations were made along the lines mentioned above, and at the end of the period a summary was entered in the record which gave the results of rest in bed and the patient's progress while at rest. This was expressed in graphic form when practicable, showing in this way any tendency toward improvement, or the reverse, and the *rate* of progress.

The length of this period of observation was determined by the special circumstances in each case. After a satisfactory estimate of the effect of rest could be made, the observation period was terminated; and, without changing any other factor, a large amount of digitalis was given in a short period of time. Observations were then continued in the same manner as before. Any pronounced changes which resulted could reasonably be attributed to the administration of digitalis. The graphs were particularly valuable in determining *any change in rate* of progress.

The digitalis used was a stock tincture which has repeatedly been shown to possess a high degree of potency. It was not restandardized. No arbitrary rule was followed in determining the amount to be administered. In general, an estimate was made of the total dose as determined by the Eggleston method for an average tincture, and an amount somewhat smaller than this estimated dose was chosen. This was done because experience with the tincture used had shown that its potency was high. This "chosen dose" was administered in divided doses, usually about one half being given at once and smaller portions administered at intervals for the next twelve to twenty-four hours. If nausea or other evidence of toxic action appeared, the drug was stopped.[9] In no case was a large amount given to a patient who might have received digitalis within three weeks.

The records of pulse, weight and urine output were made by the nurse. Those of blood pressure and vital capacity were made by the clinical clerk assigned to the case. Notes on the heart, size of the liver, amount of edema and patient's symptoms, together with the summary at the end of the observation period, and a similar note after the administration of digitalis, were made by myself.

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9. One patient (Case 9) received an additional dose after nausea and vomiting. This case receives comment below.

About forty patients were studied. In many cases certain quantitative observations were not made, and some of the results, therefore, are equivocal because of insufficient data. Such cases are not included in this series. The series does include, however, every case record which contains data sufficient to warrant a conclusion as to the effect of digitalis in the individual case, irrespective of any result that might have been anticipated from observation of similar cases. The records of twenty cases are thought to be complete enough to satisfy this condition. Incomplete cases are excluded irrespective of any result that might have been suggested by the incomplete data recorded. It may be stated here that these discarded records are of great value in that the evidence which they give is strongly confirmatory of the soundness of the conclusion arrived at from a study of those cases whose records are more complete, and which are recorded below.

RESULTS

In order to save space and to make convenient a comparison of the records before and after the administration of digitalis, these twenty case records are given in tabular form. The table (Table 1) gives the record of each patient as follows: In the first column are shown the case number, age, Wassermann reaction, and diagnosis. Column two gives the physical signs on examination of the heart and the electrocardiographic findings. Column three gives, in order, the number of days in hospital, hospital result, number of days the patient was kept under observation before digitalis was adminstered, the amount of the tincture that was given and the number of hours over which the administration of this amount of the drug was distributed. In the fourth column are noted the evidences of digitalization. Following this are recorded the patient's symptoms, pulse rate, amount of edema, vital capacity, size of liver, weight, renal tests, etc., amount of urine, blood pressure, and "remarks." The three parallel columns give such record: on admission, O.A.; for the observation period, O.P., and for the period after the administration of digitalis, A.D.

The records of these twenty cases, selected solely on the basis of completeness of data, give an unmistakable answer to the main problem at hand. Digitalis affected most of these cases favorably. The favorable effects included diuresis (with attendant loss of edema, decrease in the size of the liver and loss of weight), rise of vital capacity and improvement of symptoms. In many cases these results were most impressive.

The accompanying figures, which reproduce some of the records given in the table, give these results, as far as practicable, in graphic form, and thus show the effect of digitalis on the *rate of progress*. The effect on symptoms, which was often most striking, cannot, of course, be represented in this way.

TABLE 1.—*Data Showing*

Case Number: Age: Wassermann Test: Diagnosis	Heart: Electrocardiogram	Days in Hospital: Result: Observed: Digitalis	Evidences of Effect		Symptoms	Pulse Rate: Extremes	Mean	Tendency
1. 50 years. Negative. Chronic myocarditis, arteriosclerosis, decompensation	Sounds weak. Left ventricle preponderant, T upright in all	22 days. Improvement. 7 days. 20 c.c., 9 hours	T negative in all; left ventricular premature contractions	O A	Cheyne-Stokes' sign; dyspnea; nausea	.....	...	.....
				O P	No improvement; Cheyne-Stokes' sign	83–123	100	No
				A D	Sudden improvement; no Cheyne-Stokes' sign	(3) 68–102 (6) 60–90	86 78	Down No
2. 22 years. 4 plus. Aortic insufficiency, decompensation	To and fro murmur at aortic. Normal	39 days. Improvement. 8 days. 17 c.c., 10 hours	Nausea	O A	Dyspnea; cough; pain in chest			
				O P	Marked improvement	88–120	100	No
				A D	Progressive improvement	(4) 85–108 (4) 72–100	95 86	No Down
3. 61 years. Negative. Chronic myocarditis, chronic nephritis, decompensation	Systolic at apex. T negative in I; R notched in II	23 days. Improvement. 13 days. 21 c.c., 12 hours	Nausea, vomiting; T lowered in I, II and III; ventricular extrasystoles	O A	Dyspnea; weakness	.....	...	.....
				O P	Considerable improvement; no dyspnea	60–105	80	No
				A D	More rapid improvement	64–96	82	.....
4. 54 years. Negative. Chronic myocarditis, chronic nephritis, premature contractions A and V, decompensation	Sounds distant. T iso-electric in I and II	50 days. Died. 17 days. 22 c.c., 24 hours	Increase in number of premature contractions A and V	O A	Dyspnea	.....	...	.....
				O P	Fluctuated	75–105	90	No
				A D	Fluctuated	65–105	88	.....
5. 39 years. 4 plus. Aortic insufficiency, chronic nephritis, aortitis (syphilitic), decompensation	Diastolic at left sternal border, systolic and diastolic at apex	33 days. Died. 10 days. 12 c.c., 12 hours	Nausea, vomiting, premature contractions	O A	Swelling of abdomen; dyspnea; orthopnea	.....	...	.....
				O P	Improvement	60–130	92	No
				A D	Fluctuated	80–100	85	Down
6. 43 years. Negative. Aortic insufficiency, chronic myocarditis, decompensation	..... T negative in I and II; P-R, 0.2	20 days. Improvement. 10 days. 12 c.c., 12 hours	Nausea, vomiting, T lowered in I, II and III; P-R, 0.23	O A	Dyspnea; palpitation	.....	...	.....
				O P	Improvement	(7) 75–112 (3) 70–88	100 80	Down
				A D	Progressive improvement	60–100	78	.....
7. 23 years. Negative. Chronic valvular disease, mitral stenosis and insufficiency, premature contractions, decompensation	Diastolic rumble and thrill at apex; bigeminy; fibrillation (auricular)	67 days. Improvement. 33 days. 10 c.c., 12 hours	None	O A	Cough; dyspnea; palpitation; dizziness	.....	...	.....
				O P	Very slight improvement; normal mechanism	112–140	120	.....
				A D	Decided improvement	112–132	120	.....
8. 44 years. Negative (14 cells, spinal fluid). Aortic insufficiency, chronic (syphilitic) myocarditis, arteriosclerosis, decompensation	To and fro murmur at aortic, left sternal border and apex. T negative in II and III	22 days. Improvement. 10 days. 12 c.c., 24 hours	Nausea (toxic rhythm) interpretation ?; T lower in III	O A	Pain in epigastrium; dyspnea; nausea; cough	80	...	.....
				O P	Marked improvement	68–96	78	Up
				A D	Improvement (progressive); after, toxic	72–90 *(98)	82	.....

The numbers in parentheses at the left give the number of days over which observations were made. Parentheses at pulse, after digitalis administration, for three days were 68 to 102, mean 86; for six days, 60 to 90, mean 78. The weight

Edema	Vital Capacity, C.c.	Liver (Cm. Below Costal Margin)	Weight, Kg.	Other Findings	Amount of Urine, C.c.	Blood Pressure: Extremes	Blood Pressure: Mean	Blood Pressure: Tendency	Remarks
Slight	.....	15	86.3	PSP, 15%; NPN, 57.8; Alb., 4 gm.	.....	190 / — / 150			Result as striking as ever seen in auricular fibrillation
None	2,750 (2) 2,800 (1) 3,000 (0)	10 (4) 8+ (0)	88 (0)	Less albumin and casts	340-1,140	172-196 / 132-160	185 / 145		
None	3,925 (5) 4,400 (10)	Rapid decrease	77.6 (2)	.....	4,700 (1)	190-210 / 105-100		S up / D down	
Moderate	.....	14 (?) 9 (?)	68.6	.....	.....	.....			Improvement progressive; not definitely influenced by digitalis
None	.....	4	74.7	PSP, 90%; NPN, 38	About 700 per day	120-170 / 30- 60	125 / 40	down / down	
None	.....	4	?	.....	About 700 per day	140 / — / 20	1st day; then slow fall		
Marked	.....	19	113	Trace albumin; PSP, 40%; NPN, 42.7	.....	.....			Rapid decrease in liver; diuresis; loss of weight; improvement in symptoms
Diminished	Rose from 1,400 to 2,500 in 8 days	8 (2)	95	PSP, 65%; NPN, 26	About 850 per day	140-115 / 95- 70	120 / 85	down / down	
No note	Continued rise to 3,200 in 5 days	3 ? (1) 4 ? (1)	93 (1)	.....	1st 12 hours not collected, "an awful lot;" 2d 12 hours 1,100	150 / — / 85	1 day; rapid fall		
Marked	750	9½	84.5	Alb. and casts; PSP, 40%; NPN, 60	Urine not accurately measured	130 / — / 110			Evidence of pulmonary thrombosis at time of digitalis administration
Slight decrease	750 to 1,250	8	81.5 (1)	.....		120-134 / — / 100-105	128 / — / 103	down / — / down	
No change	650 to 1,100	8	80 (20)	.....	No apparent increase	210 / — / 175	thrombosis		
Moderate	1,300	9¼	.....	Alb. and casts; PSP, 20%; NPN, 41	.....	145 / — / 65			Began to lose ground five days after digitalis
No change	1,050 to 1,100	6¾	.....	.....	About 500 per day				
Fluctuated	1,000 to 1,200	Slight progressive decrease	.....	.....	About 600 per day				
Moderate	.....	10	85	Alb. and casts; NPN, 35.7	.....	165 / — / 87			Measurements do not show when liver decreased; rise of vital capacity
None	1,100 (6) 1,200 (3) 1,750 (2)	No note	80.6 (3)	.....	About 700 per day				
None	1,200 (1) 1,700 (5)	Not enlarged	76.3 (4)	.....	About 700 per day				
Marked	450	11	.....	NPN, 76	.....	.....			Question of previous digitalis poisoning; later toxic with subsequent improvement
Same	450 to 550 450 (1)	.....	.....	NPN, 33	.....	95 / — (3) / 80			
Much less	500 (3)	8½(7)							
Moderate	1,300	3	68.4	Slight albumin; PSP, 55%; NPN, 36	.....	160 / — / 90			Relieved of symptoms under rest; no definite effect from digitalis; toxic; rise in blood pressure
None	Rose to 2,900 in 7 days	0	63 (2) (in 7 days)	No albumin	About 600-1,200	160-120 / 90- 70		Down / Down	
None	Rose to 3,100 in 5 days	0	61.4 (0) 59 (2)	Faint trace of albumin (2) (3)	About 450-1,160	130 / — (2) / 90		Down / Down	

the right show the day on which the accompanying observation was made; that is, in the first case, the extremes of on the day of administration was 88 kg.; two days after digitalis weight was 77.6 kg.; * indicates isolated observation.

TABLE 1.—*Data Showing Case*

Case Number: Age: Wassermann Test: Diagnosis	Heart: Electrocardiogram	Days in Hospital: Result: Observed: Digitalis	Evidences of Effect		Symptoms	Pulse Rate: Extremes	Pulse Rate: Mean	Pulse Rate: Tendency
9. .... 52 years (II) Negative Chronic myocarditis, chronic nephritis, arteriosclerosis, decompensation	First sound prolonged at left sternal border R notched in I; T negative in I; P-R, 0.2	94 days Died 7 days 17.5 c.c., 25 hours	Extreme nausea, some vomiting; discomfort; auriculoventricular dissociation; auricular, 131; ventricular, 162; change in ventricular complex	O A	Slight dyspnea; nausea and vomiting	.. ..	...	.....
				O P	Little, if any, improvement	(2) 78–110 (4) 72– 90	90 80	Down No
				A D	(2) Worse	.....	...	.....
					(8) Some improvement	*(60) 70–100	... 81	.....
10. ..... 58 years Negative Chronic myocarditis, mural thrombi left and right ventricles, decompensation	Systolic at apex P-R, 0.16; QRS, 0.11; T negative in I	108 days Died 7 days 10 c.c., 10 hours	P-R, 0.2	O A	Dyspnea; palpitation; Cheyne-Stokes' sign	105	...	.....
				O P	Slight improvement; Cheyne-Stokes' sign	(5) 58–108 (2) 80	95	Down
				A D	Improvement in dyspnea; Cheyne-Stokes' sign	70–110	78	.....
11. .... 63 years Negative Emphysema, chronic bronchitis, arteriosclerosis	No abnormal heart findings Electrocardiogram normal; P-R 0.18	83 days Improvement 16 days 11 c.c., 5½ hours	Nausea and vomiting; T lower in III (?)	O A	Long attacks of coughing; dyspnea	.....	...	....
				O P	Slight improvement	74–100	85	.....
				A D	No improvement	72– 96	85	..
12. .... 57 years Negative Chronic nephritis, chronic myocarditis, arteriosclerosis	First sound impure at apex; 2d sound reduplicated	31 days Improvement 16 days 10 c.c., 7 hours	Nausea and vomiting; T lower in II	O A	Dyspnea; weakness; headache; nausea; vomiting	.....	...	....
				O P	Stronger; less dyspnea; no vomiting	(5) 78–140 (11) 72– 95	92 85	Down
				A D	Progressive improvement	72– 93	82	.....
13. .... 52 years (II) Negative Chronic myocarditis, chronic nephritis, decompensation	Soft systolic at apex; sounds faint; left ventricular premature contractions T iso-electric in all	35 days Improvement 16 days 21 c.c., 24 hours	Nausea and vomiting; P-R lengthened 0.05; R less shaded	O A	Dyspnea; weakness; insomnia	70	...	.....
				O P	(9) Improvement	*(120) 78–108	96	No
					(7) Stationary	*(60) 70–105	89	.....
				A D	Improvement	(4) 92– 98 (7) 68– 90	78 76	.....
14. .. .. 46 years Negative Chronic myocarditis, chronic nephritis, decompensation	Faint systolic all areas; gallop; all complexes low T negative in I and III	35 days Improvement 8 days 16 c.c., 16 hours	Vomiting; A-V dissociation; rapid A and V; ectopic beats; bigeminy	O A	Dyspnea; dizziness; palpitation	.....	...	.....
				O P	Some improvement; still severe	73–120	95	No
				A D	Much nausea; rapid improvement after 7 days	(2) 75–120 (3) 85–105 (10) 72– 95	... 96 87	.....

Edema	Vital Capacity, C.c.	Liver (Cm. Below Costal Margin)	Weight, Kg.	Other Findings	Amount of Urine, C.c.	Blood Pressure: Extremes; Mean; Tendency	Remarks
Marked	.....	12 ?	.....	Albumin, 2 plus; PSP, 10%; NPN, 62	.....	230 / 130	Toxic with delayed diuresis and loss of weight and rise of vital capacity
Moderate	2,000 (1)	12½ (1)	84 (0)	NPN, 54 (2)	1,100-1,600 1,350; no tendency	230-210; 215 / 140-130; 130	
Moderate	3,000 (1) 3,000 (2)	6¾ (2)	83 (1) 82 (2)	.....	400 700	140 / 100 — (1); 190 / 130 — (2)	
None	Rise to 3,600	6¾ (3) 8½ (10)	82 (3) 73.1 (10)	NPN, 53	1,000-4,300 2,581	200 / 120 — (3); 210 / 135 — (10)	
Slight	2,000	7	66	Trace albumin; NPN, 59	.....	160 / 88	Under two courses of digitalis, vital capacity rose to 2,300; later, while up, and small doses of digitalis, was 3,200
None	2,300 (1)	5½ (4) 4½ (0)	72.6 (1)	Trace albumin; NPN, 45 (1)	(3) 500-850 (3) 1,150-1,300	152-160; 158 / 88-106; 100	
None	1,800 (1) 1,800 (4) 2,300 (7)	0 (4)	67 (1) 64 (2)	No albumin (3); NPN, 40 (4)	3,100 (1) 1,725 (2)		
None	.....	3	.....	No albumin; PSP, 65%	.....	100 / 60	Not a cardiac case; rise in blood pressure, systolic and diastolic; slight loss of weight
None	2,800 (4) 2,700 (2)	3	48.1 (4) 48.6 (0)	No albumin NPN, 34	.....	(7) 115-130; 118 / 70-95; 80	
None	2,750 (2) 2,800 (5) 2,800 (7)	.....	46.8 (2) 46.8 (8)	No albumin	.....	155 / 85 — (1) 160 / 92 — (3)	
None	.....	6	.....	Albumin; PSP, 20%; NPN, 66	.....	.....	Temporary rise of blood pressure only definite effect; rise of vital capacity ?
None	1,300 (14) 1,500 (9) 1,675 (1) 1,850 (0)	6 (1)	48.1 (5)	Less albumin; NPN, 43	470-1,000	(7) 196-215 / 100-105	
None	1,950 (1) 2,000 (3) 1,950 (5) 1,700 (7)	.....	50 (1) 50.4 (7)	Continued less albumin	No apparent change	230 / 112 — (1)	
Marked	1,650	11½	109.1 (14)	Trace albumin; PSP, 30%; NPN, 43	.....	120 / 90	Three stages: (a) improvement, (b) stationary (rest), (c) digitalis
Moderate	Rose to 2,500	8½ (8)	98.7 (6)	Trace albumin	500-1,000 average 800	120-135; 125 / 90-95; 90 — No / No	
Moderate	2,000 (6) 2,400 (1)	8 (1)	98.4 (0)	Moderate albumin	600-925 average 700		
None (4)	2,500 (2) 3,400 (7) 3,600 (10)	8 (1) 7 (3) 7 (17)	93.1 (1) 88.6 (2)	Trace albumin	2,000 in 2d 12 hours 2,350 (4)	135 / 90 — (0); 140 / 90 — (1)	
Moderate	800	.....	.....	Albumin plus; PSP, 5%; NPN, 45	.....	.....	10 c.c. at 8 p. m.; diuresis that night; toxic; delayed symptomatic improvement
Moderate	Rose to 1,200 (0)	.....	86.3 (3) 85.4 (0)	Less albumin	500-1,150 average 600 no tendency	115-132; 125 / 95-110; 105 — No / No	
Rapid disappearance	1,150 (3) 1,200 (6) 1,400 (10) 1,300 (14)	.....	75 (4)	Albumin declined with diuresis	3,200 (1) 1,900 (2)	(8) 140-155 / 105-116	

TABLE I.—*Data Showing Case*

Case Number: Age: Wassermann Test: Diagnosis	Heart: Electrocardiogram	Days in Hospital: Result: Observed: Digitalis	Evidences of Effect		Symptoms	Pulse Rate: Extremes	Pulse Rate: Mean	Pulse Rate: Tendency
15..... 46 years Negative Chronic nephritis, chronic myocarditis, arteriosclerosis, decompensation	Low systolic at aortic and apex; gallop; few premature contractions	27 days Improvement 7 days 14 c.c., 24 hours	Nausea and vomiting	O A	Dyspnea; cough; weakness; dizziness	.....	...	.....
				O P	Improvement in dyspnea and cough	85–120	102	No
				A D	Rapid improvement	(3) 84–108 (4) 72–100	94 86	No Down
16..... 39 years Negative Chronic nephritis, adenoma of kidney, atheroma of coronary, chronic myocarditis	Soft systolic at apex; A second impure T negative in I and II	40 days Died 19 days 15 c.c., 10 hours	Nausea and vomiting	O A	Headache; failing vision	.....	...	.....
				O P	Marked improvement	(12) 80–112 (7) 80–96	94 86	Down No
				A D	Continued to feel well	76–98	86	.....
17..... 40 years 3 plus Syphilitic myocarditis, aortitis, decompensation	Loud systolic at apex and base T negative I, II and III	44 days Improvement 7 days 18 c.c., 23 hours	Disappearance of nausea	O A	Dyspnea; vomiting; pain in epigastrium	.....	...	.....
				O P	No improvement	(4) 74–98 (3) 74–97	82 86	No
				A D	Less dyspnea; less nausea	(2) 73–100 (4) 80–90	86 86	.....
18..... 48 years 4 plus Chronic (syphilitic) myocarditis, arteriosclerosis, decompensation	Systolic at apex; diastolic at aortic two weeks after digitalis T negative in I; QRS 0.12 in II and III	32 days Improvement 7 days 10 c.c., one dose	Nausea and vomiting; T lowered in I; negative in II	A O	Dyspnea; cough; weakness	.....	...	.....
				O P	No improvement; Cheyne-Stokes' sign developed	84–100	90	No
				A D	Prompt relief of all symptoms	(2) 78–90 (3) 72–78	82 70 63	Down Down
19..... 43 years Negative Chronic myocarditis, chronic nephritis, dilatation of aorta, decompensation	Systolic at all areas	14 days Improvement 9 days 12 c.c., 24 hours	.....	O A	Pain in abdomen and chest; dyspnea; insomnia	.....	...	.....
				O P	Some improvement	(5) 68–106 (4) 68–90	100 80	Down Down
				A D	Rapid improvement	65–80	78	.....
20..... 57 years Negative Chronic myocarditis, chronic nephritis, decompensation	Soft systolic at apex T negative in I and II; P-R, 0.2; R shaded	24 days Improvement 7 days 13 c.c., 17 hours	Nausea and vomiting; T lowered in I	O A	Dyspnea; cough; pain in epigastrium	.....	...	.....
				O P	Some improvement	60–76	68	Up
				A D	Rapid improvement	66–80	72	.....

Edema	Vital Capacity, C.c.	Liver (Cm. Below Costal Margin)	Weight, Kg.	Other Findings	Amount of Urine, C.c.	Blood Pressure: Extremes; Mean; Tendency	Remarks
None	1,650	5¾	.....	Albumin plus; casts; R.B.C.; PSP, 15%; NPN, 67	.....	210/130	5 c.c. at noon, 5 c.e. at 6 p.m.; diuresis that day; improvement with no visible edema
None	Fell to 1,400 (6)	5¾	73.1 (6)	Less albumin	650–1,000 no tendency	222–195 / 140–124; 215 / 135; No / Up	
None	2,300 (1) 2,500 (4) 2,500 (5)	2¾ (2) 0 (7)	70.4 (2)	.....	1,500 1st 12 hours	(5) 230–250 / 150–205	
None	2,300	0	.....	Albumin, 10 gm.; PSP, 10%; NPN, 111	.....	225/155	No effect except nausea; suggestive fall of blood pressure
None	2,400 to 2,900 2,800	0	64.3 (9)	Albumin, 2.5 gm.; NPN, 95	1,300–2,400 average 2,200	(10) 185–190 / 135–140	
None	2,400 to 2,900 2,800	0	63.6 (5)	.....	(5) 750–1,100 (intake smaller)	(2) 170–175 / 118–135 (3) @ 180/125	
"None"	1800	8	.....	Albumin plus; PSP, 37%	....	145/70	Progressive fall in blood pressure
"None"	1,900 (5) 2,000 (3) 2,300 (6)	9 (1)	80.8 (2) 81 (6)	.....	....	140–160 / 70–80 Down / Down	
¼ to 1.5 cm. decline in measure	2,200 (1) 2,300 (4) 2,400 (5)	6 (6)	75 (4)	.....	....	(7) 130–140 / 55–70	
Moderate	.....	10	.....	Albumin plus; PSP, 40%; NPN, 32	.....	....	10 c.c. at 8 p.m.; diuresis that night; no morphin for first night in a week; remarkable immediate result
Moderate (same)	1,700 (5) 1,900 (4) 1,700 (2) 1,800 (6)	8¾ (9)	84.5 (4) 84.5 (6)	.....	300–800 average 500 no tendency	183–195 / 120–142; 188 / 130	
None (3)	2,100 (2) 2,500 (3) 2,740 (4) 2,800 (6)	0 (3)	79.6 (1) 74.5 (2) 72.7 (3)	Trace albumin (15)	5,200 (1) 2,600 (2)	190/125 (1) 155/90 (2 and 12)	
Slight	....	"At umbilleus"	68.2	Albumin plus	.....	.....	Average result
A little less	2,900 (4) 2,700 (5) 2,500 (6)	6 (6)	69.2 (1) 68.2 (6)	Less albumin	375–850 average 600 no tendency	135–140 / 105–115 No / No	
Much less (1); none (5)	2,800 (1) 3,000 (2) 3,200 (3)	4.5 2 (2)	67.4 (1) 65.6 (2) 64.3 (4)	.....	2,600 (1) 1,950 (2)	155/125 (6) 170/115 (1)	
Moderate	....	11	76	Much albumin; casts; NPN, 45.4; PSP, 50%	....	230/96	Average result
Some diminution	1,900 (6) 2,000 (3) 2,300 (1) 2,400 (6)	9 (6)	75 (1) 74.6 (6)	.....	525–1,400 average 800 no tendency	230–185 / 95–85 Down / No	
Rapid diminution	2,500 (1) 2,700 (2) 2,500 (4)	5 (2) 0 (3)	75 (1) 72.1 (2)	.....	2,200 (1) 3,450 (2)	215/85 (1 and 2) 180/85 (9)	

Figure 1 thus represents graphically the data recorded for the eighth case of Table 1. In this, and in the other figures, the solid dots represent systolic blood pressure; the smaller rings, diastolic blood pressure; the larger rings connected by the heavy broken line, vital capacity expressed in cubic centimeters; the blocks, weight in kilograms; the vertical columns at the base, urine in cubic centimeters; the horizontal lines, mean pulse rate; "L" represents the extent of the liver in centimeters below the costal margin in the midclavicular line; and the dotted column shows the time of digitalis administration.

It will be noted that during ten days' rest there was a fall in blood pressure and in weight, a decrease in size of the liver, and a rise in vital

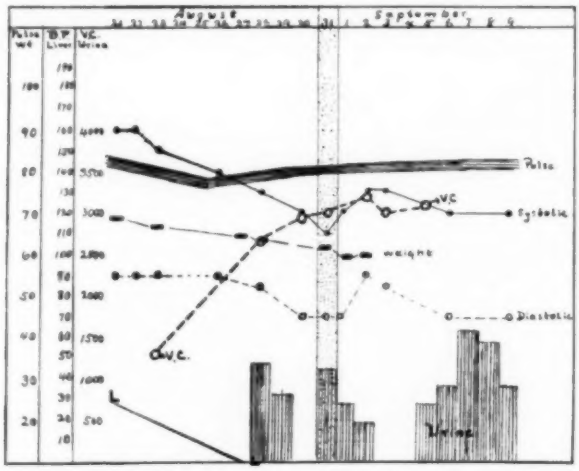

Fig. 1 (Case 8).—Effect of rest.

capacity. If digitalis had been given at the time this patient was put to bed, improvement might easily have been attributed to the drug. There is, however, little evidence that he was favorably affected by it.

Figure 2, which reproduces the record of the third case of Table 1, shows loss of weight and rise of vital capacity after digitalis administration, but at a rate which was not changed by the drug. It will be observed, however, that the liver, which after an initial diminution had remained stationary in size previous to the administration of the drug, underwent a rapid further shrinkage subsequent to digitalis administration.

A similar, though less rapid, effect on the liver is shown in Figure 3 (tenth case of the table).

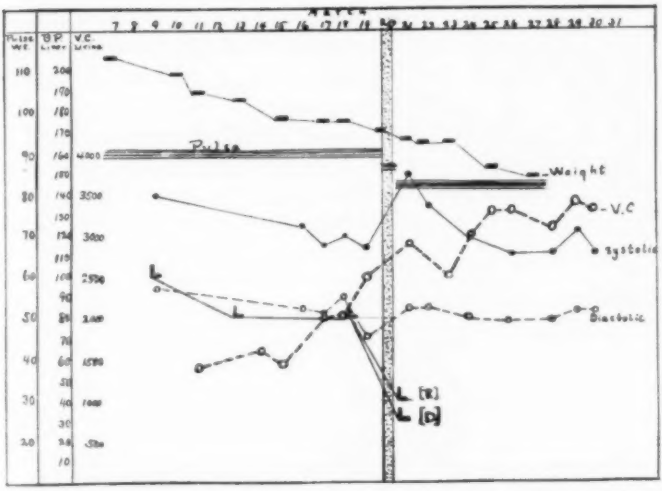

Fig. 2 (Case 3).—Principal effect on liver. *R* indicates resistance; *D*, dulness.

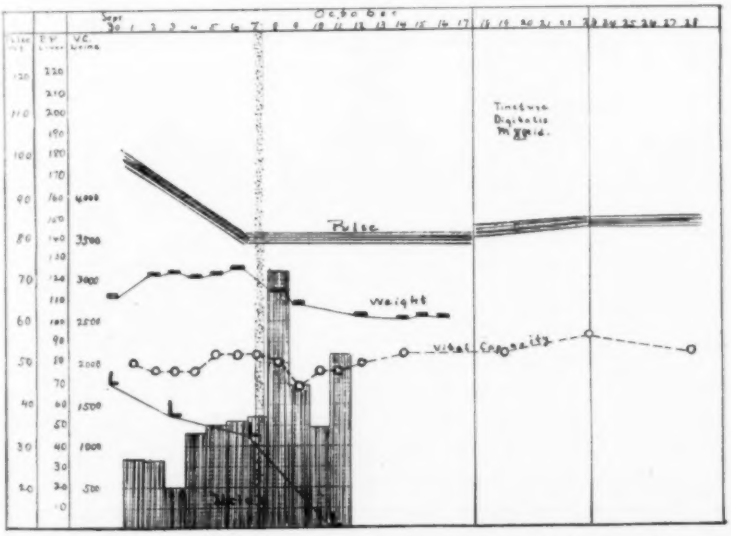

Fig. 3 (Case 10).—Diuresis. loss of weight, no rise of vital capacity.

This patient showed also a considerable diuresis and loss of weight, but without an increase in vital capacity. It will be noted that the pulse rate, which had steadily declined during the observation period, showed no further fall at the time of the diuresis and symptomatic improvement.

Figure 4 (Case 1 of Table 1) shows a loss of 10.4 kg. in weight in two days, with a diuresis of proportional extent. The most striking results in this patient cannot be represented graphically. The decrease in thickness of the liver was remarkable. This organ had presented a visible tumor which had diminished a little in size during observation.

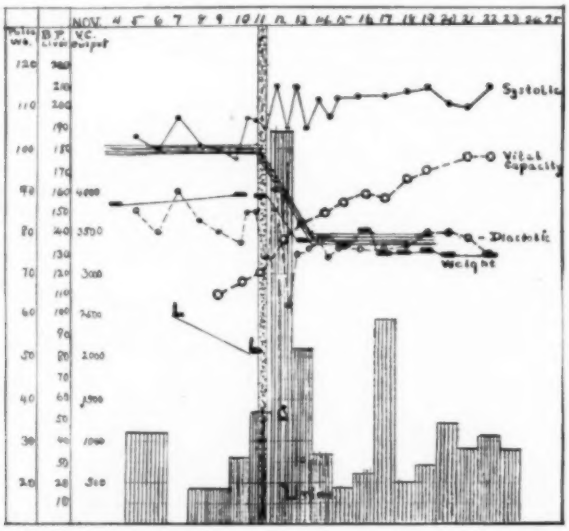

Fig. 4 (Case 1).—Diuresis, loss of weight, rapid decrease of liver, rise of vital capacity (sudden relief of symptoms).

Within forty-eight hours after the administration of digitalis the liver could still be felt by deep palpation, but instead of a visible mass in the upper abdominal quadrant there was a depression beneath the margins of the rib on both sides. The symptomatic improvement also was sudden and most impressive. He received 12 c.c. of the tincture at 9 a. m. That afternoon for the first time during the week of his stay in the hospital he had no dyspnea and no Cheyne-Stokes respiration. These symptoms did not return during his subsequent stay in the hospital. No more remarkable result from digitalis administration had ever come under our observation in any patient irrespective of whatever cardiac mechanism may have been present.

The thirteenth case, the graphic record of which is given in Figure 5, presents evidence which is most convincing of the effects of digitalis. It will be seen that during a period of nine days this patient improved under rest in bed. His weight decreased 10.4 kg.; there was a decrease in the size of the liver, a rise in vital capacity and an improvement in symptoms. Following this, for a period of about a week, his condition was stationary; there was little decrease in the liver, no appreciable change in weight, no rise of vital capacity and no further symptomatic improvement. He was then given 21 c.c. of tincture of digitalis within twenty-four hours. There was a prompt diuresis, loss of weight (9.8

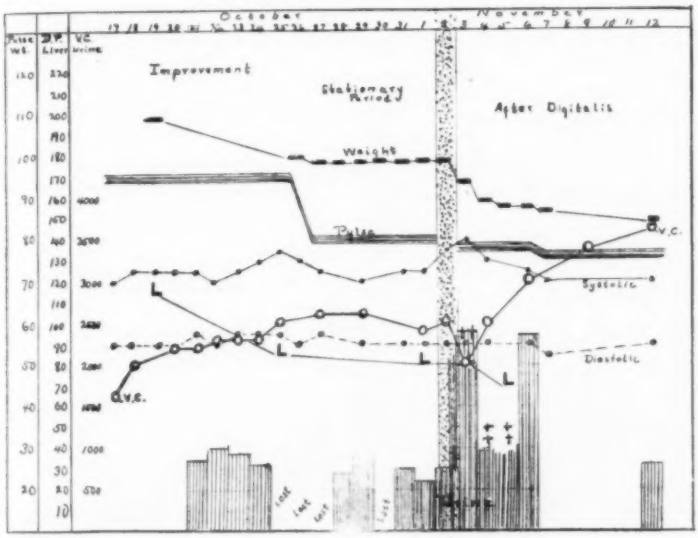

Fig. 5 (Case 13).—Improvement under rest, a succeeding stationary period and a further sudden effect from digitalis. Amounts of urine after digitalis are incomplete.

kg. in forty-eight hours), rise of vital capacity and improvement in symptoms. Not all of the urine was collected, the incomplete data being indicated by the + marks in the figure.

The eighteenth case (Fig. 6) showed a relief from symptoms which was as sudden and remarkable as were the other effects that are recorded graphically. Because this case presented some unusual features and was, at the same time, most convincing of the strikingly beneficial effects of digitalis, a summary of the case is published, together with the chronological notes that were made in the history at the time of study.

A. P., a colored man, aged 48, married, a Pullman porter, was admitted to the hospital on Feb. 14, 1923; he was discharged on March 18, 1923, improved. The diagnosis was: syphilis; myocarditis, chronic (syphilitic); hypertrophy of the heart; dilatation, chronic cardiac; cardiac decompensation; aortitis (syphilitic); general arteriosclerosis. The Wassermann test was four plus; repeated (same). There was no fever.

The patient's chief complaints were dyspnea, cough, edema and weakness. He had had a few attacks of sore throat twenty years before and an occasional winter cough for six or seven years; he had not had rheumatism. He had had gonorrhea ten years before and a primary sore twelve years before of two weeks' duration. He had suffered from weakness for three or four months; also a cough which had been worse for the past four weeks. He had had dyspnea for four weeks and a slight dyspnea four months before. Edema had been present for three weeks.

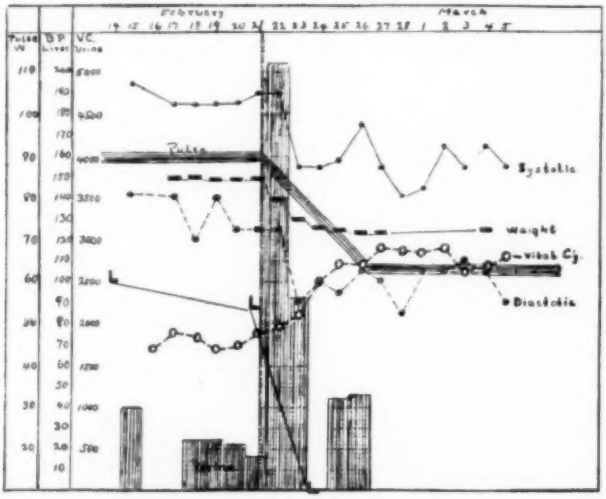

Fig. 6 (Case 18).—Diuresis, loss of weight, shrinkage of liver, rise of vital capacity (sudden relief of symptoms).

Condition on Admission.—When admitted to the hospital he had orthopnea and moderate edema. The liver extended 10 cm. below the costal margin. There was a soft systolic murmur at the apex and over the precordium. There was dulness at the base of the right lung. The vital capacity was 1,700. The phenolsulphonephthalein excretion was 40 per cent. The blood pressure was: systolic, 196; diastolic, 112. The maximum heart dulness was 14.5 cm. in the sixth intercostal space; 2.5 cm. to the right in the fourth space.

The urine contained 1.5 gm. of albumin. There were finely granular and hyaline casts. The electrocardiogram showed "T" depressed in I; QRS, 0.1 of a second; P-R, 0.15 of a second. There was left ventricular preponderance. The nonprotein nitrogen content was 32.2 mg.

Treatment and Course.—The patient was put to bed and given medium nephritic diet. Fluids were limited to 2,000 c.c.

Feb. 21, 1923: After seven days' observation, the patient said his short breathing was "just the same." His cough was a little better. The pulse had

shown no tendency to fall—perhaps a tendency to rise a little. The blood pressure was about constant. The weight was constant. The vital capacity showed no tendency. The liver was fairly definite at 8.75 cm. below the costal margin, a slight decrease. He had Cheyne-Stokes respiration. There was moderate edema of the legs and slight edema of the abdominal wall. The heart apex was in the sixth intercostal space, about 15.5 cm. to the left; there was a long, low systolic murmur here, lower at the left sternal border. There was slight dulness at the right base and a few moist râles at both bases. There had been little, if any, improvement. Cheyne-Stokes respiration had developed. The patient had had no "doctor's medicine" during the past five weeks. Tincture of digitalis was ordered as follows: (estimated dose would be 26 c.c. without allowance for edema) 10 c.c. at 8 p. m., 3 c.c. at 10 a. m., 3 c.c. at 1 p. m.; total, 16 c.c.

Feb. 22, 1923, 9:30 a. m.: Asked how he was, the patient said "sick." He was nauseated, but did not vomit. Asked how he felt, aside from nausea, he said "better," with emphasis. He said that he passed "five times as much urine" during the past night as during the previous night. He said he had not been "short of breath" during the past night for the first time since entrance. He had received 10 c.c. of tincture of digitalis at 8 p. m. on Feb. 21, 1923. The output for the twelve hours was 2,500 c.c.; his weight during the forenoon of February 21 was 186 pounds (84.5 kg.); on the forenoon of February 22 he weighed 175¼ pounds (79.6 kg.). The liver was 8.25 cm. below the costal margin (about the same as yesterday). The apex beat was regular, 86; there was considerable visible edema.

The reaction to digitalis had been as remarkable as it usually is in cases of auricular fibrillation. (A note to this effect was made thirteen and one-third hours after administration.) An electrocardiogram had not been made. The vital capacity was 1,975. The blood pressure was: systolic, 185; diastolic, 125. The past night was the first of seven consecutive nights that the patient had not received morphin, which was ordered to be given when necessary. Remainder of digitalis was to be omitted.

Feb. 23, 1923, 9 a. m.: The patient said he was nauseated; he had vomited a few times the preceding day. His respiration varied in intensity, but not rhythmically—there was no apnea. The abdominal and the chest walls were thinner. There was slight edema around the ankles and lower tibia. He had not slept well on account of pain in the upper part of the right side of the abdomen; but there had been no coughing or dyspnea. The liver was less easy to feel; apparently it was 6 cm. below the costal margin; it had gone down. The apex beat was forceful in the fifth intercostal space—13.25 cm. to the left. There was a soft systolic murmur there, louder at the base. The patient said that he felt better except for the pain. He had a slight cough, but no dyspnea.

Feb. 24, 1923, 10:30 a. m.: The patient was asleep. When awakened he said that he felt very well and that he had slept "very good." He had had little cough and no dyspnea since digitalis was administered. He had had no pain in the region of the liver since the previous day. The liver could not be felt; there was some resistance in the right upper quadrant. There was dulness about 1 cm. below the costal margin, a remarkable decrease in two days. There was no edema or nausea.

Summary: There had been a rapid relief from symptoms (pain in the liver region for one day) and a loss of 22 pounds (10 kg.) in two days. There had been diuresis, loss of edema, shrinkage of the liver, and a rise of vital capacity—200 c.c. in two days. There was a sudden drop of blood pressure on the second day (30 points). There was as complete and striking relief as in fibrillators, with no considerable reduction in the apex rate—not more than 10 beats a minute, if that many.

TABLE 2.—*Results in Condensed Form*

Descriptive Data								Result									
No.	Diagnosis	Blood Pressure	Pulse	Edema	Enlarged Liver	Wassermann Test	Hospital Result	Loss of Edema	Loss of Weight	Diuresis	Liver Smaller	Rise in Vital Capacity	Improvement Symptoms	Pulse[7] Lower	Blood Pressure Rise	Blood Pressure Fall	Remarks
1	Chronic myocarditis, decompensation	185/145	100	(Yes)[1]	Yes	Negative	Improvement	Yes	Yes	Yes	Yes	Yes	Yes	Yes (14)	S (8)	D	Sudden relief
2	Aortic insufficiency, decompensation	120/ 30	100	(Yes)[1]	Yes	4 plus	Improvement	None	Yes ?	No	No	..	No (p)[3]	Yes (5)	S (1)	..	
3	Chronic myocarditis, chronic nephritis, decompensation	130/ 85	90	Yes	Yes	Negative	Improvement	No note	Yes	Yes	Yes	No (p)[3]	Yes	Yes (8)	S (1)	..	Remarkable liver shrinkage
4	Chronic myocarditis, chronic nephritis, decompensation	128/103	90	Yes	Yes	Negative	Died	No	..	No	No	No	No	No (2)	S (1) D (1)	..	Pulmonary thrombosis
5	Aortic insufficiency, decompensation	145/ 65	92	Yes	Yes	4 plus	Died	No	..	No	No (p)[3]	No	No	Yes (7)	..	..	
6	Aortic insufficiency, chronic myocarditis, decompensation	165/ 87	80	(Yes)[1]	Yes	Negative	Improvement	None	No (p)[3]	No	?	Yes	No	No (2)	..	..	
7	Chronic valvular disease, stenosis and insufficiency, decompensation	95/ 80	120	Yes	Yes	Negative	Improvement	Yes	..	..	?	Yes	Yes	No	..	..	Auricular fibrillation after subsequent digitalis
8	Aortic insufficiency, decompensation	120/ 70	78	(Yes)[1]	(No)[5]	Negative 14 cls.	Improvement	None	Yes	No	.. (.)[3]	No (p)[4]	No (p)[4]	No[6]	S (1) D (1)	..	Toxic; improvement with rest
9	Chronic myocarditis, chronic nephritis, decompensation	215/130	80	Yes	Yes	Negative	Died	No Yes	Yes Yes	No Yes	Yes Yes	? Yes	No Yes ?	.. No	.. ..	S (1) D (1)	Toxic rhythm; improvement delayed
10	Chronic myocarditis, mural thrombi, decompensation	158/100	80	(Yes)[1]	Yes	Negative	Died	None	Yes	Yes	Yes	No	Yes	No (2)	..	..	Improvement with no rise in vital capacity
11	Emphysema, chronic bronchitis	118/ 80	85	No	Yes	Negative	Improvement	None	Yes	....	....	No	No	No	S (s) D (s)	..	Not a cardiac case
12	Chronic nephritis, chronic myocarditis	210/108	85	No	Yes	Negative	Improvement	None	No	No	....	No	No (p)[4]	No (3)	S (1) D (1)	..	Not decompensated
13	Chronic myocarditis, chronic nephritis, decompensation	125/ 90	80	Yes	Yes	Negative	Improvement	Yes	Yes	Yes	Yes ?	Yes	Yes	No (2)	S (1)	..	A, improvement with rest; B, stationary period; C, improvement with digitalis
14	Chronic myocarditis, chronic nephritis, decompensation	125/105	95	Yes	?	Negative	Improvement	Yes	Yes	Yes	....	No (p)[4]	Yes (d)[5]	No	S (s) D (s)	..	Toxic; mixed result
15	Chronic nephritis, chronic myocarditis, decompensation	215/135	102	No	Yes	Negative	Improvement	None	Yes	Yes	Yes	Yes	Yes	Yes (8)	S (s?) D (s?)	..	Diuresis, loss of weight; no visible edema
16	Chronic nephritis, small granular kidneys, atheroma coronary	185/135	86	No	No	Negative	Died	None	No	No	( )	No	No	No[6]	..	S (1) D (1)	Not a cardiac case
17	Chronic myocarditis, aortitis, decompensation	140/ 70	86	"No"[2]	Yes	3 plus	Improvement	"Yes"[2]	Yes	....	Yes	No	Yes	No[6]	No change		
18	Chronic myocarditis, aortitis, decompensation	188/130	90	Yes	Yes	4 plus	Improvement	Yes	Yes	Yes	Yes	Yes	Yes	Yes (8);(20)	.	S (s) D (s)	Sudden remarkable effect
19	Chronic myocarditis, chronic nephritis, decompensation	138/110	80	Yes	Yes	Negative	Improvement	Yes	Yes	Yes	Yes	Yes	Yes	No (2)	S (1) D (1)	..	Average result
20	Chronic myocarditis, chronic nephritis, decompensation	195/ 90	68	Yes	Yes	Negative	Improvement	Yes	Yes	Yes	Yes	No (p)[3]	Yes	No[6]	S (1)	.	Average result

[1] indicates that edema disappeared during observation; [2], no visible edema, but measurements decreased after digitalis; [3], liver decreased during observation; [4], pulse was higher than before administration of digitalis; [5], pulse fell after

Feb. 25, 1923: The patient was quite comfortable and did not complain. The liver was not felt; there was dulness about 2 cm. below the costal margin. There was a soft systolic murmur at the apex and base of the heart.

March 2, 1923: The patient had been allowed to sit up a few minutes each day. Twenty minims of tincture of digitalis once daily was ordered.

March 16, 1923: There was a heaving impulse at the apex in the fifth intercostal space below and outside of the nipple, and a soft blowing systolic murmur. At the aortic area there was a definite, fairly loud, not prolonged diastolic murmur, occurring immediately after the second sound. There was also a soft systolic murmur in the aortic area. The systolic murmur was a little louder at the left sternal border, but no diastolic murmur was heard there. The edge of the liver descended from beneath the costal margin on deep inspiration. No edema was present.

In order to obtain some notion of the constancy of these results and to determine, as far as possible, in what class of cases they occur, a second table was constructed (Table 2). It is a summary of Table 1. It furnishes a brief description of each patient, giving the diagnosis, mean blood pressure, mean pulse rate, findings concerning edema and enlargement of the liver, the Wassermann reaction and the hospital result. Under "Result" is recorded whether or not, as a result of digitalis administration, there was a loss of edema, loss of weight, diuresis, diminution in the size of the liver, rise of vital capacity, improvement of symptoms, lowered pulse rate and rise or fall of blood pressure. The answers to these questions are derived not from impression but from the quantitative data recorded in Table 1. The cases are arranged in the same order in the two tables.

The foregoing charts and tables show that in certain cases there was a prompt diuresis (with loss of weight, loss of edema and decrease in the size of the liver) as a result of digitalis administration in large dosage. Improvement in symptoms was often sudden and impressive. In many cases there were changes in pulse rate and in blood pressure.

TYPE OF PATIENTS AFFECTED

In order to throw some light on the question of the classes of patients with normal rhythm that are improved by the administration of digitalis, cases with similar findings were arranged in groups, and notation was made as to how many of each group were improved and how many not improved.

Table 3 shows that of ten patients with "chronic myocarditis" who showed edema and signs of cardiac decompensation without aortic disease and with negative Wassermann reactions, nine were improved, one not improved. Two patients with chronic nephritis, four with aortic insufficiency and edema, and one with chronic bronchitis and emphysema showed little evidence of improvement from digitalis. Two patients with myocarditis who were probably syphilitic, and one patient with mitral disease, all of whom gave evidences of decompensation, were improved by the drug.

This question was approached in still another way. A table was made which divides the cases into two groups, those who were "Improved" and those who were "Not Improved" (Table 4).

It is at once apparent from a glance at this table that the type of patient who was improved by digitalis belongs in the category of those with "chronic myocarditis," or, to employ a term that is becoming more generally used, "myocardial insufficiency," such patients exhibiting dyspnea on exertion, an enlarged and dilated heart usually with a systolic murmur at the apex, enlarged liver and edema. The hospital

TABLE 3.—*Cases Arranged in Groups with Results in Each Group*

Group	Case Number	Result	
		Improvement	No Improvement
I. Chronic myocarditis	1, 3	1, 3	..
No suspicion of syphilis	4, 9	9	4
No aortic disease	10, 13	10, 13	..
Decompensated	14, (15)	14, 15	..
Edema when admitted	19, 20	19, 20	..
Total number	ten	nine	one
II. Chronic nephritis, no edema	12, 16	.....	12, 16
Total number	two	.....	two
III. Aortic insufficiency	2, 5	.....	2, 5
Decompensated	6, 8	.....	6, 8
Edema when admitted			
Total number	four	.....	four
IV. Mitral disease, edema, decompensated	7	7	.....
Total number	one	one	.....
V. Emphysema and chronic bronchitis, no edema, not decompeasated	11	.....	11
Total number	one	.....	one
VI. Myocarditis, probably syphilitic, decompensated	17, 18	17, 18	.....
Total number	two	two	.....

diagnosis in Case 7 was "valvular disease, chronic cardiac, mitral stenosis and insufficiency." The patient presented, however, in addition to the usual evidences of mitral disease, the characteristic features above mentioned.

The patients in Cases 1 and 10 had had edema, but it had disappeared during the observation period. Both doubtless still had excess tissue fluid, however, for after digitalis administration both lost weight and had diuresis. The face of one (Case 1) was noticeably much thinner in appearance after administration of the drug.

The patient in Case 15 had no apparent edema. Notwithstanding this, he lost 2.7 kg. in weight in two days after receiving digitalis. Unfortunately, his rate of loss (if any) before digitalis was not observed. His urine output for the first twelve hours after administra-

TABLE 4.—*Comparing Cases that were "Improved" with those that were "Not Improved" by Digitalis*

No.	Diagnosis	Wassermann Test	Aortic	Edema	Hospital Result	Loss of Edema	Loss of Weight	Diuresis	Liver Smaller	Rise in Vital Capacity	Improvement in Symptoms
					Improved						
1	Myocarditis; decompensation....	0	0	(Plus)[1]	Improvement	Yes	Yes	Yes	Yes	Yes	Yes
3	Myocarditis; nephritis; decompensation.....	0	0	Plus	Improvement	....?	Yes	Yes	Yes	No (p)[3]	Yes
7	Chronic valvular disease; mitral; decompensation	0	0	Plus	Improvement	Yes	....	....	?	Yes	Yes
9	Myocarditis; nephritis; decompensation.....	0	0	Plus	Died	Yes	Yes	Yes	Yes	Yes	Yes ? [4]
10	Myocarditis; decompensation.....	0	0	(Plus)[1]	Died	None	Yes	Yes	Yes	No	Yes
13	Myocarditis; nephritis; decompensation.....	0	0	Plus	Improvement	Yes	Yes	Yes	Yes?	Yes	Yes
14	Myocarditis; nephritis; decompensation.....	0	0	Plus	Improvement	Yes	Yes	Yes	?	No (p)[3]	Yes
15	Nephritis; myocarditis; decompensation.....	0	Systolic	(0)	Improvement	None	Yes	Yes	Yes	Yes	Yes
17	Myocarditis; aortitis; decompensation.....	Plus	Systolic	Plus ?[2]	Improvement	"Yes"[2]	Yes	....	Yes	No	Yes
18	Myocarditis; aortitis; decompensation.....	Plus	??	Plus	Improvement	Yes	Yes	Yes	Yes	Yes	Yes
19	Myocarditis; nephritis; decompensation.....	0	0	Plus	Improvement	Yes	Yes	Yes	Yes	Yes	Yes
20	Myocarditis; nephritis; decompensation.....	0	0	Plus	Improvement	Yes	Yes	Yes	Yes	No (p)[3]	Yes
					Not Improved						
2	Aortic insufficiency; decompensation.....	Plus	Diastolic	(Plus)[1]	Improvement	None	Yes?	No	No	....	No (p)[3]
4	Myocarditis; nephritis; decompensation.....	0	0	Plus	Died	No	....	No	No	No	No
5	Aortic insufficiency; decompensation.....	Plus	Disatolic	Plus	Died	No	....	No	No (p)[3]	No	No
6	Aortic insufficiency; decompensation.....	0	Diastolic	(Plus)[1]	Improvement	None	No (p)[3]	No	?	Yes	No
8	Aortic insufficiency; decompensation.....	0 (14 cl)	Diastolic	(Plus)[1]	Improvement	None	Yes	No	Had disp'd	No (p)[3]	No
11	Emphysema; bronchitis.....	0	0	0	Improvement	None	Yes	....	....	No	No
12	Nephritis; myocarditis.....	0	0	0	Improvement	None	No	No	....	No	No (p)[3]
16	Nephritis; atheroma, coronary.....	0	0	0	Died	None	No	No	Not enlg'd	No	No

[1] indicates that edema had disappeared during observation; [2], no visible edema, measurements decreased after digitalis; (p)[3], change was progessive; [4], toxic effect, beneficial effects delayed.

tion of digitalis was 1,500 c.c. It seems probable that he had excess fluid in the tissues which was not extensive enough to cause pitting on pressure.

The patient in Case 17 showed no pitting. The ankle measurements, nevertheless, increased a little during the observation period, and her weight increased slightly, while following digitalis administration the ankle measurements decreased, and she lost weight.

If the patients in Cases 15 and 17, then, be regarded as having had edema when admitted to the hospital, it may be stated that all of the twelve patients who were improved by administration of digitalis showed evidence of cardiac decompensation with edema of greater or less extent. They belonged, with the exception of Case 7, to the group that is usually called "myocardial insufficiency."

Of the eight patients who were "not improved," those in Cases 11 and 16 did not have cardiac disease, while nephritis appeared to be responsible for the symptoms in Case 12. Four had aortic disease. The remaining patient that showed no improvement (Case 4) belonged in the same category as those who showed improvement, that is, myocardial insufficiency. His condition, however, was grave on admission. His vital capacity at no time was higher than 1,230 c.c. He had, moreover, evidences of pulmonary thrombosis at the time of digitalis administration, and he died seven weeks later.

The patients with aortic insufficiency were not improved. The conclusion that no such cases may be benefited by digitalis, however, is not warranted from the study of such a small number of cases. The patient in Case 8 improved rapidly under rest. Had he received digitalis before the disappearance of the edema and before his improvement, these results might have been more rapid. He exhibited, moreover, a toxic rhythm and other evidences of toxic effect which may have prevented favorable action. There is little positive evidence, however, from these four cases, that digitalis is of value in cases of aortic insufficiency. Case 18 is of much interest in this connection. This case record, given above, shows that it was only about three weeks after digitalis administration that signs of aortic disease were noted. There was at that time a diastolic murmur at the aortic area. There were, however, no other evidences of aortic insufficiency. It would seem probable that the symptoms were due chiefly to syphilitic myocarditis, and that the aortic involvement was early.

MECHANISM OF ACTION

There remains for consideration the question of the mechanism by which digitalis (in large dosage) produces diuresis, disappearance of edema, decrease in size of the liver and improvement of symptoms in cases of myocardial insufficiency. The results in cases of this type have

been so uniform when large amounts of the drug have been given in a short time interval, whereas previous results from smaller dosage had been without benefit, that the question arises whether the rapid disappearance of edema is not a result of some physical or chemical reaction on the body fluids rather than of an effect on the heart or kidneys. When the subject of edema is better understood, the solution of this question will be nearer.

Certain observations in this study, however, offer strong evidence that the beneficial effects that followed the administration of digitalis to the patients with myocardial insufficiency were the result of some sort of action of the drug on the heart. This explanation is indicated by the rapid diminution in size of the liver, and is further supported by a study of a patient who showed toxic effects of rather high degree after digitalis administration.

This patient (Case 9 in Table 1) had received a massive dose of digitalis with strikingly favorable results about nine months previously (Case 1 in Table 1). On his last admission, after eight days' observation, he received tincture of digitalis as follows: at 5 p. m., August 29, 5 c.c.; at 10 a. m., August 30, 5 c.c.; at 1 p. m., 5 c.c., and at 6 p. m., 2.5 c.c. Before receiving the last dose he vomited and felt worse than he had felt for some days. Following the last dose he was uncomfortable and had almost constant nausea. The next day, August 31, his blood pressure had fallen from systolic 200, diastolic 130, to systolic 140, diastolic 100. He looked much worse. Electrocardiograms showed nodal rhythm (transient) after the second dose (August 30), and a-v dissociation with an auricular rate of 131 and ventricular rate of 162 on August 31 (Fig. 7). During the succeeding days electrocardiograms showed abnormal rhythms and a gradual return to normal on September 8.

Figure 10 shows that there was a diuresis which increased in amount during the time that the toxic effects were wearing off his heart and which reached a maximum on September 8, the day his heart rhythm became normal. Edema had disappeared by September 9. This case will be reported more in detail, together with other toxic rhythms resulting from digitalis, in a subsequent paper. The important point for present consideration is that there was an early decrease in the size of the liver, which occurred before the full amount of digitalis had been received; that there was a toxic action on his heart, and that during the time when this was of high degree he had no diuresis; but that he began to have diuresis as his heart recovered, and that there was extreme diuresis which was delayed only so long as his heart showed the toxic effects of the drug. It is difficult to escape the conclusion that this diuresis with loss of weight and of edema was due to the action of digitalis, and that its delay was due to the lowered efficiency of his

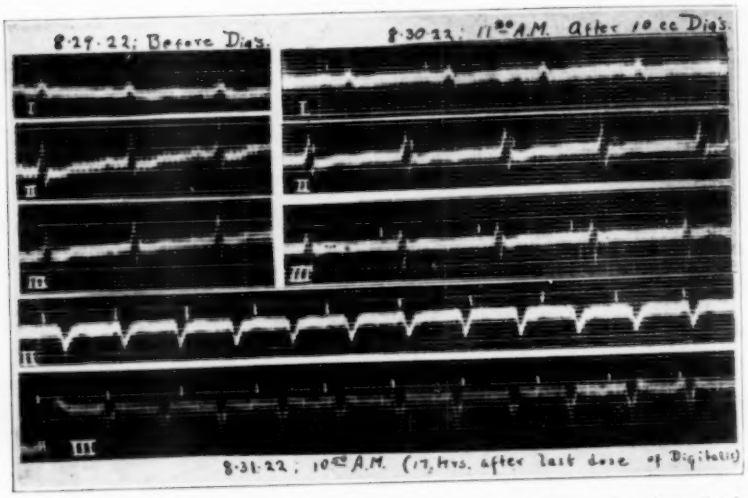

Fig. 7.—Electrocardiograms of Case 9. The first shows the three leads before digitalis was started. The second shows nodal rhythm in Lead II. The third shows a-v dissociation with auricular and ventricular tachycardia of different rates. Note the change in complexes. The position of the "P" waves is indicated by markers.

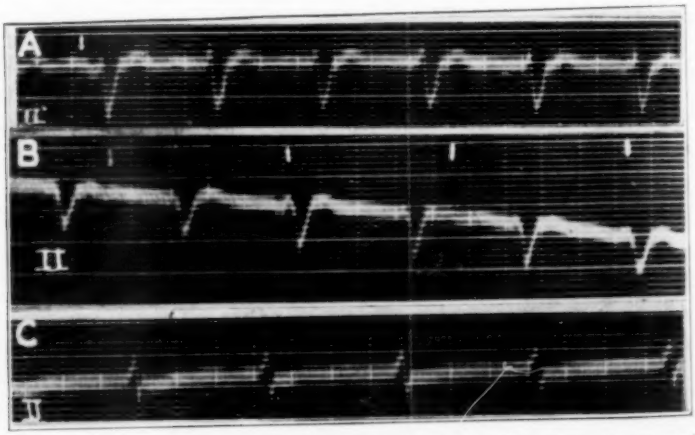

Fig. 8.—Electrocardiograms of Case 9; Lead II. The first shows nodal rhythm; the second, a-v dissociation with slower auricular rate; the third, complex of same type as before digitalis, but still a-v dissociation. The Lead A was made on Sept. 1, 1922, at 11 a. m.; that in B on Sept. 1, 1922, at 3 p. m.; that in C on Sept. 4, 1922.

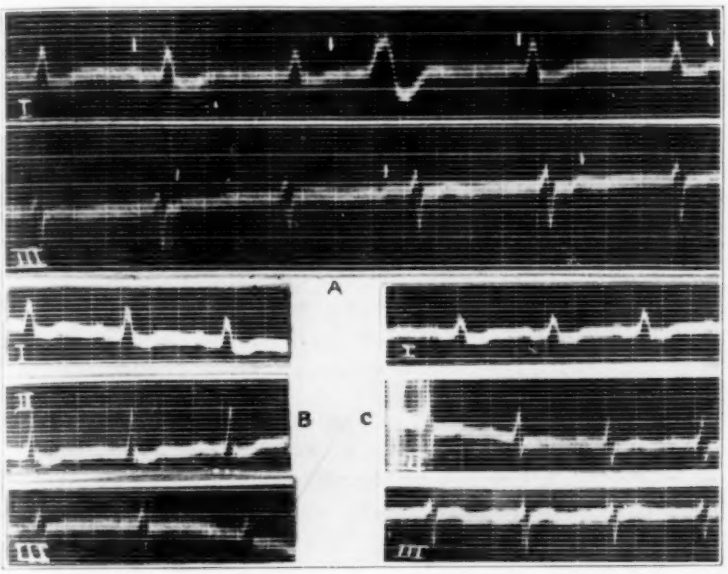

Fig. 9.—Electrocardiograms of Case 9. The first shows complete heart block. The others show normal mechanism. The leads in A were made on Sept. 7, 1922; those in B on Sept. 8, 1922; those in C on Sept. 9, 1922.

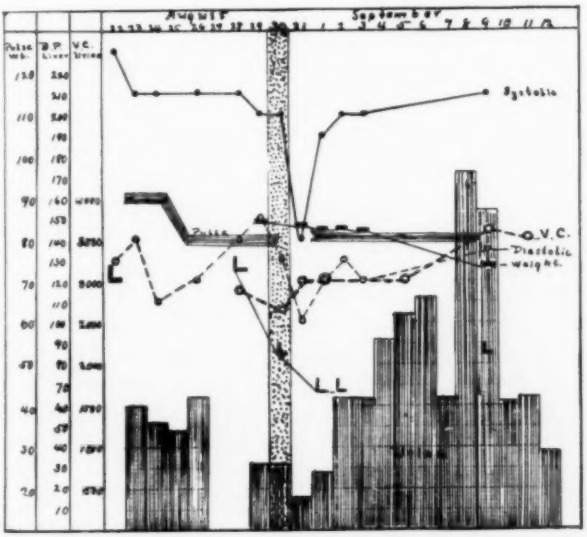

Fig. 10 (Case 9).—Toxic effect; delayed diuresis and loss of weight.

heart while that organ was suffering the extremely toxic effects of the drug. In other words, the evidence is that digitalis acted directly on the heart and in some way *increased its efficiency* after the (temporary) ill effects had disappeared.

It has long been known that there is an action of the drug on the heart besides its effect on the conducting tissues between auricle and ventricle. The questions have been: (1) Just what is this action? (2) Is it beneficial or not?

In this series, about thirty patients with myocardial insufficiency showed, with great uniformity, diuresis and symptomatic improvement after rapid digitalization. This fact per se does not prove that these beneficial results were due to a cardiac action of the drug. But we know that the drug has a cardiac action; and in one case that was carefully followed the beneficial effects did not appear until evidences of harmful effect on the heart had disappeared. There must be, then, some action of digitalis, besides its effect on the conducting tissues, by virtue of which it increases cardiac efficiency in these cases. What is this action? This question has been the subject of many careful experimental studies, and further comment here could add nothing toward its solution.

It should be stated, however, that this beneficial action appears to be independent of any slowing in ventricular rate in cases with normal mechanism. There is still much confusion on this subject of slowing. Eggleston,[5] in 1915, regarded slowing as an evidence of the effect of digitalis on cases with normal mechanism. In 1920, he says[10] that it "generally produces considerable slowing" in "those cases of heart failure in which marked oedema is present" but that with this and one other exception "the therapeutic administration of digitalis is seldom followed by a significant degree of slowing of the heart rate in the presence of the normal sinus rhythm." With the latter part of this statement most careful observers are now in agreement, although one not infrequently meets practitioners who still expect slowing from digitalis administration to patients with sinus rhythm.

Our observations indicate that even in patients with marked edema whose mechanism in normal slowing is not a characteristic attendant on improvement, and that even when it occurs it follows the diuresis and is a result rather than a cause of the improvement. The patients in this series whose heart rate previous to digitalis administration was fast (above 80) quite commonly showed a decline in rate to about 80 after improvement. Those who were improved by the drug but had had a slow rate before its administration, showed no further slowing with improvement (Table 1, column showing mean pulse rate; also

10. Eggleston, Cary: Some Newer Concepts in Digitalis Therapy, Am. J. M. Sc. **160**:625 (Nov.) 1920.

Figures 2, 3 and 4). The improvement in Case 10 (Fig. 3) was clearly not associated with a change in rate. The rate had declined spontaneously until the day before digitalis administration, but showed no fall with his sudden improvement at that time. The patient in Case 13 (Fig. 5) showed a much greater spontaneous drop in rate following improvement with rest than he showed at the time of his pronounced improvement from digitalis. In the former instance, his rate declined from 95 to 80, while at the time of digitalis administration (and marked diuresis) there was a further reduction in rate to only 78. Case 18 (Fig. 6) showed a considerable fall in rate subsequent to, rather than at the time of, sudden improvement (see note of February 24). Case 20 (Table 1) showed a well marked result from digitalis. The patient's mean heart rate, however, was only 68 before the administration of the drug, but was showing an upward trend. This upward tendency continued, and the mean rate after digitalis was 72—a normal rate.

Slight spontaneous changes in rate were common in all these cases, and were as frequent among those who were not improved as among those patients that showed diuresis and symptomatic improvement. It would seem clearly indicated, therefore, that slowing is not an integral factor in the improvement in these cases, and that when it does occur it is rather a subsequent readjustment to improved conditions of the circulation, which would take place after marked improvement from any cause.

BLOOD PRESSURE

There was no uniform effect on blood pressure. By far the commonest result was a temporary rise of systolic pressure (Table 2). Quite frequently the diastolic pressure also was raised, and the tendency appeared to be for this diastolic rise also to be temporary. In a few instances the elevation of both was sustained. In one patient who showed a greatly beneficial effect from the drug (Case 1, Fig. 4) there was a sustained rise of systolic pressure, with a sustained fall of the diastolic. Another patient whose improvement was most impressive (Case 18) showed a delayed fall of both the systolic and diastolic readings, which were sustained.

The rise of systolic pressure that usually occurred was never great. There appeared to be no relationship between the original level of pressure and its course after digitalis. Whether or not the patient was improved by the drug appeared to bear no relationship to the change in blood pressure.

CONCLUSIONS

1. Tincture of digitalis, when given by mouth in large doses over a short time interval, affects favorably certain patients with normal heart rhythm.

2. The favorable effects are: improvement in symptoms, diuresis, loss of edema and decrease in size of liver.

3. The patients in whom these effects occur with most consistency belong to the class known as "myocardial insufficiency."

4. The improvement from digitalis in these cases does not depend on change in ventricular rate.

5. This improvement is probably due to increased muscular efficiency brought about by the action of the drug on the heart muscle.

6. Patients with myocardial insufficiency improve under proper digitalis administration in about the same proportion of cases as do patients with auricular fibrillation. The improvement in the former class of cases is usually, perhaps, of somewhat less extent, but it is frequently as impressive as the most striking results that occur in patients with fibrillation of the auricles.

7. It should be stated here that certain manifestations of toxic action, which will be reported in greater detail, were observed with sufficient frequency to indicate that the method of rapid digitalization that was employed in this study is not without danger. The dosage used was doubtless, in many cases, above the optimum amount.

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BOOK REVIEWS

LA DÉGÉNÉRESCENCE HÉPATO-LENTICULAIRE. Maladie de Wilson Pseudo-Sclérose. Par H. C. Hall, Ancien Chef de clinique à l' "Hôpital de Bispebjaerg," Copenhague. Créface du Professeur Pierre Marie. Paper. Price, 20 francs, net. Pp. 361, with 44 illustrations. Paris: Masson et Cie, 1921.

This is the most complete monograph on the subject of lenticular degeneration that has yet appeared. Hall first gives a brief review of Wilson's four cases and a summary of the clinical features of the syndrome called by Wilson "progressive lenticular degeneration." He then correlates the Westphall-Strümpell pseudosclerosis with Wilson's syndrome; he believes that the corneal pigmentation noted in many cases of pseudosclerosis is of frequent occurrence in progressive lenticular degeneration, although it was overlooked by Wilson. He next reports four cases of his own and the histories of three other patients provided by the courtesy of his confréres in Copenhagen. Four of these patients belonged to one family, and two others were brothers. In the review of these seven cases he expresses his opinion that one case was an example of true Wilson's disease; that Cases 2 and 3 were pseudosclerosis, and that Cases 4 to 7 form a familial group of a nervous disease resembling Wilson's syndrome, with hypertonia as the most intensive symptom. We feel that the data supplied by Hall for the last group are too incomplete to warrant this assumption.

The author next tabulates the sixty-eight cases in the literature of Wilson's disease and pseudosclerosis: of the patients, fifty were males and eighteen females. The duration of the twenty-two fatal cases varied from two to seven years. Corneal pigmentation was only looked for in thirty-seven cases and was found to be present in twenty-one, or more than 50 per cent.; of these thirty-seven cases, only nine were Wilson's disease, and in three of them (those of Pollock, Soederbergh, Hall, Case 1) corneal pigmentation was observed. Hall, therefore believes that the corneal pigmentation is pathognomonic of both Wilson's disease and pseudosclerosis, and not merely of the latter syndrome.

Speech is variously affected, the condition ranging from mere dysarthria to complete anarthria. Involuntary movements and hypertonia are common symptoms: besides these, contractures, associated movements, ataxia, adiadokokinesis, epileptiform and apoplectiform crises are observed. While the tendon reflexes are usually normal, Babinski's phenomenon was noted in twelve cases.

While the deep and superficial sensation is intact, the gait is affected and of a peculiar character due to the hypertonia and tremors. The electrical reactions are normal. The mental state is more or less affected. The cerebrospinal fluid was normal except in two cases, in which a slight pleocytosis existed. The liver may be found decreased and the spleen increased in size. Alimentary levulosuria has been demonstrated in four cases; urobilinuria is not constant, however. Glycosuria was present in six cases. The skin may show pigmentation, as was noted in six cases. Postmortem a nodular cirrhosis was an absolutely constant feature both in true Wilson's disease and pseudosclerosis. So far as the anatomic alterations in the nervous system are concerned, Stoecker and Hall have found all transitions between the picture described by Wilson in his progressive lenticular degeneration and those described by Alzheimer in the Westphal-Strümpell pseudosclerosis. Hall, therefore suggests a common name for the two syndromes, namely, "hepatolenticular degeneration." These cases belong to the heredofamilial nervous diseases which enter into the Gowers concept of abiotropic affections.

MODERN ASPECTS OF THE CIRCULATION IN HEALTH AND DISEASE. By CARL J. WIGGERS, M.D., Professor of Physiology in the School of Medicine of Western Reserve University. Second edition. Thoroughly revised. Price $7.50. Pp. 661, with 204 engravings. Philadelphia and New York: Lea & Febiger, 1923.

In the present work, the first edition which was favorably received eight years ago has been thoroughly revised. The charters have been extended and much valuable material has been added in the new ones on "The Efficiency and Adaptability of the Heart," "Vascular Control of the Circulation," "The Principles and Practice in Optical Registration of Mechanical Pulsations in Man" and "The Dynamic Consequences of Chronic Heart Disease." The general plan of the original edition has been retained. The book is divided into three sections. The first deals with the physiology of the circulation, the second with graphic methods for the clinician and the third with disease of the heart and circulation.

The physician is constantly becoming more aware of the importance of a thorough basic knowledge of physiology in the interpretation of clinical problems. The applications of physiologic methods in recent years have been chiefly responsible for the rapid advancement in our knowledge of the heart. The author of the present work is one of the foremost authorities on the physiology of the circulation. He has personally investigated many phases of the subject and is thoroughly familiar with the entire field. Those interested in the cardiovascular system will greatly appreciate Dr. Wigger's second edition. The clinician may raise the objection that some of the subjects are considered briefly in the section on disease of the heart and circulation. In this connection it may be added that this section was evidently not intended to be an exhaustive consideration of the subject, as might be implied by the subject, but to correlate so far as possible the normal and pathologic physiology. In this respect, the author has satisfactorily accomplished his aim.